indicated by the claims when viewed in light of the specifications and prosecution histories. An order setting forth these constructions will accompany this opinion.

BIACORE, AB, and Biacore, Inc., Plaintiffs,

v.

THERMO BIOANALYSIS CORP., Defendant.

No. CIV.A.97–274 SLR.

United States District Court, D. Delaware.

Dec. 30, 1999.

Owner of patent for biosensor matrix coating sued competitor for infringement. The District Court, Robinson, J., held that: (1) patent was infringed; (2) patent was not invalid as anticipated or obvious; (3) parent patent satisfied written description requirement; (4) proper measure of damages was reasonable royalty; and (5) neither enhanced damages nor award of attorney fees was warranted.

Ordered accordingly.

1. Declaratory Judgment ⇨232, 233

Case or controversy is jurisdictional predicate for declaratory judgment of patent noninfringement or invalidity. U.S.C.A. Const. Art. 3, § 2, cl. 1; 28 U.S.C.A. § 2201.

2. Declaratory Judgment ⇨345.1

In order for court to retain jurisdiction over counterclaims seeking declaratory judgment of patent noninfringement and invalidity once patentee withdraws allegation of infringement, defendant must establish by preponderance of evidence that it has reasonable apprehension that it will be sued on nonasserted claims. U.S.C.A. Const. Art. 3, § 2, cl. 1; 28 U.S.C.A. § 2201.

3. Declaratory Judgment ⇨234

Patentee's withdrawal of infringement claims did not deprive court of jurisdiction over defendant's counterclaims seeking declaratory judgment of noninfringement and invalidity, where patentee had not stipulated to noninfringement; defendant retained reasonable apprehension of suit. U.S.C.A. Const. Art. 3, § 2, cl. 1; 28 U.S.C.A. § 2201.

4. Patents ⇨226.6

Literal patent infringement exists when claim, as construed by court, reads on accused device exactly.

5. Patents ⇨226.6

Patent infringement may not be avoided simply by adding features or components not required by claims.

6. Patents ⇨312(1.1)

Plaintiff has burden of demonstrating literal patent infringement by preponderance of evidence.

7. Patents ⇨165(3)

Patent claim construction begins with claim language, which defines scope of claim.

8. Patents ⇨157(1)

In analyzing patent claim language, court must employ normal rules of syntax.

9. Patents ⇨161, 162

In construing patent claim, court must ascribe meaning to any technical term used in claim that it would be given by persons experienced in field of invention, unless it is apparent from patent and prosecution history that inventor used term with different meaning.

10. Patents ⇨159, 168(2.3)

Neither patent's prosecution history nor any extrinsic evidence considered can

enlarge, diminish, or va
claims.

11. Patents ⇨101(11)

Dependent claims in
sensor matrix coating w
by-process claims, and th
pass identical products fo
processes; independent
tions of coating, incorpor
dent claims, reflected s
tions, and not process b
was obtained.

12. Patents ⇨165(4)

Patent claim pream
that claim as a whole sugg

13. Patents ⇨165(4)

Generally, patent
when read in context of
cites claim limitations onl
be read independently
preamble must be read to
claim or is essential to po

14. Patents ⇨165(4)

Patent claim's pre
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fining matrix coating oth
in claim; thus, preamble
scope of claim.

15. Patents ⇨235(2)

Accused device litera
ent claims for biosenso
even if accused devic
formed by different se
claims did not require pa
of steps. 35 U.S.C.A. § 2

16. Patents ⇨312(8)

Although proof of in
other's patent infringeme
state claim for inducemer
is not required; rather, c
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17. Patents ⇨259(2)

Manufacturer of
coating that literally inf
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. Art. 3, § 2, cl. 1; 28
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Judgment 🔑234
withdrawal of infringement
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9, 168(2.3)
ent's prosecution history
evidence considered can

enlarge, diminish, or vary limitations in claims.

11. Patents 🔑101(11)

Dependent claims in patent for biosensor matrix coating were not product-by-process claims, and thus could encompass identical products formed by different processes; independent claim's descriptions of coating, incorporated into dependent claims, reflected structural limitations, and not process by which coating was obtained.

12. Patents 🔑165(4)

Patent claim preamble has import that claim as a whole suggests for it.

13. Patents 🔑165(4)

Generally, patent claim preamble, when read in context of entire claim, recites claim limitations only if claim cannot be read independently of preamble and preamble must be read to give meaning to claim or is essential to point out invention.

14. Patents 🔑165(4)

Patent claim's preamble statement "suitable for use in a biosensor" informed construction of remainder of claim by defining matrix coating otherwise described in claim; thus, preamble was limitation on scope of claim.

15. Patents 🔑235(2)

Accused device literally infringed patent claims for biosensor matrix coating, even if accused device's coating was formed by different sequence of steps; claims did not require particular sequence of steps. 35 U.S.C.A. § 271(b).

16. Patents 🔑312(8)

Although proof of intent to induce another's patent infringement is necessary to state claim for inducement, direct evidence is not required; rather, circumstantial evidence may suffice. 35 U.S.C.A. § 271(b).

17. Patents 🔑259(2)

Manufacturer of biosensor matrix coating that literally infringed patent induced infringement when it sold device in which infringing coating could be used along with instructions on how to use device in manner that infringed. 35 U.S.C.A. § 271(b).

18. Patents 🔑312(4)

Patent invalidity must be proven by facts supported by clear and convincing evidence.

19. Patents 🔑314(5)

Issue of patent invalidity on ground of obviousness is question of law based on factual inquiries. 35 U.S.C.A. § 103.

20. Patents 🔑314(5)

Issues of anticipation and adequacy of written description, for purpose of determining patent invalidity, are questions of fact. 35 U.S.C.A. §§ 102, 112.

21. Patents 🔑72(1)

Anticipation, invalidating patent, is established if every element of properly construed claim is present in single prior art reference. 35 U.S.C.A. § 102.

22. Patents 🔑66(1.2)

Extrinsic evidence may be used to explain but not expand meaning of prior art reference, for purpose of determining whether patent is invalid as anticipated. 35 U.S.C.A. § 102.

23. Patents 🔑65

Anticipation may be established if missing claim element, although not explicitly present in prior art reference, is necessarily inherent in it. 35 U.S.C.A. § 102.

24. Patents 🔑66(1.12)

Patent claims for biosensor matrix coating were not anticipated by prior art references which did not teach use of reactive groups that functioned to covalently bind biomolecules which had been electrostatically concentrated. 35 U.S.C.A. § 102.

25. Patents 🔑26(1)

When obviousness is based on prior art references, there must be showing of

suggestion or motivation to modify teachings of those references; test is whether it would have been obvious to select specific teachings and combine them as did patent applicant. 35 U.S.C.A. § 103.

26. Patents ⇨16.5(1)

References within the same field as that of patented invention, which were publicly available more than one year prior to priority date, were prior art for purposes of obviousness determination. 35 U.S.C.A. § 103.

27. Patents ⇨16.25

Patent claims for biosensor matrix coating were not invalid as obvious; prior art references did not teach or suggest combination of charged and reactive carboxyl groups in biosensor, invention satisfied long-recognized need and had been commercially successful, and invention had been copied by competitor. 35 U.S.C.A. § 102.

28. Patents ⇨17(1)

Factors court should consider in determining level of ordinary skill in art, for purpose of determining obviousness of patent claim, are: (1) educational level of inventor; (2) type of problems encountered in art; (3) prior art solutions; (4) rapidity of innovation; (5) sophistication of technology at issue; and (6) educational level of active workers in field. 35 U.S.C.A. § 103.

29. Patents ⇨98, 110

For later-filed patent to be entitled to filing date of earlier patent, disclosure of earlier patent must comply with written description requirement; although claimed invention need not have been described in ipsis veris, earlier disclosure must reasonably have conveyed to one of skill in art that inventor possessed later-claimed subject matter at time patent application was filed. 35 U.S.C.A. § 112.

30. Patents ⇨99

Patent's written description requirement is separate and distinct from enablement requirement. 35 U.S.C.A. § 112.

31. Patents ⇨65, 110

Parent or grandparent patent application's disclosure can be prior art against, and anticipate claims of, later-filed application containing broader claims while still not sufficiently describing claimed invention so as to allow later-claimed invention to assert parent's filing date. 35 U.S.C.A. § 112.

32. Patents ⇨314(5)

Compliance with written description requirement for patentability is question of fact that must be determined on case-by-case basis. 35 U.S.C.A. § 112.

33. Patents ⇨112.5

To prevail on claim that patent is invalid for lack of written description, challenger must provide clear and convincing evidence that persons skilled in art would not, in reading disclosure, recognize description of claimed invention.

34. Patents ⇨167(1.1)

Patent claims may be broader than specific embodiment disclosed in specification.

35. Patents ⇨98

Disclosure in parent patent of hydrogel matrix coating for biosensors employing metal surfaces was sufficient to support claims in subsequent patent for biosensors employing non-metal surfaces; description detailed matrix's versatility and noted its applicability to variety of types of biosensors, not just those employing metal surfaces. 35 U.S.C.A. § 112.

36. Patents ⇨318(1)

In order to be entitled to lost profits, as opposed to royalties, prevailing patent infringement plaintiff must show reasonable probability that it would have made sales of infringing product "but for" infringement. 35 U.S.C.A. § 284.

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37. Patents ⇨318(4.2)

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U.S.C.A. § 284.

38. Patents ⇨312(1.7)

Prevailing patent infri
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profits, by demonstrating
fringer are only suppliers
ket. 35 U.S.C.A. § 284.

39. Patents ⇨318(4.1)

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ket value rule" is applied,
recovery of damages base
plaintiff's entire apparatus
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is basis for customer demar
§ 284.

See publication Words
es for other judicial c
and definitions.

40. Patents ⇨318(4.1)

Owner of patent for b
coating, having prevailed
claims against competitor,
reasonable royalty, rather
damages, absent showing
have made competitor's sal
infringement. 35 U.S.C.A.

41. Patents ⇨319(3)

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⇒65, 110

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:ly describing claimed inven-
allow later-claimed invention
ent's filing date. 35 U.S.C.A.

⇒314(5)

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5 U.S.C.A. § 112.

⇒112.5

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›167(1.1)

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18(1)

be entitled to lost profits,
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that it would have made
ng product "but for" in-
J.S.C.A. § 284.

37. Patents ⇒318(4.2)

Prevailing patent infringement plaintiff can show "but for" causation of its damages, for purpose of recovering lost profits, by demonstrating (1) demand for patented product, (2) absence of acceptable noninfringing alternatives, (3) marketing and manufacturing capability to exploit demand, and (4) amount of profit it would have made but for infringement. 35 U.S.C.A. § 284.

38. Patents ⇒312(1.7)

Prevailing patent infringement plaintiff can show "but for" causation of its damages, for purpose of recovering lost profits, by demonstrating that it and infringer are only suppliers present in market. 35 U.S.C.A. § 284.

39. Patents ⇒318(4.1)

Where prevailing patent infringement plaintiff seeks damages on components sold with patented apparatus, "entire market value rule" is applied, which permits recovery of damages based on value of plaintiff's entire apparatus containing several features when patent-related feature is basis for customer demand. 35 U.S.C.A. § 284.

See publication Words and Phrases for other judicial constructions and definitions.

40. Patents ⇒318(4.1)

Owner of patent for biosensor matrix coating, having prevailed on infringement claims against competitor, was entitled to reasonable royalty, rather than lost profit damages, absent showing that it would have made competitor's sales in absence of infringement. 35 U.S.C.A. § 284.

41. Patents ⇒319(3)

In evaluating egregiousness of patent infringer's conduct, for purpose of awarding enhanced damages, court must consider factors that render infringer's conduct more culpable as well as factors that are mitigating or ameliorating. 35 U.S.C.A. § 284.

42. Patents ⇒227

Actual notice of another's patent rights imposes affirmative duty of due care upon potential infringer to avoid infringement.

43. Patents ⇒319(3)

Competitor's infringement of patent for biosensor matrix coating was not willful, and thus enhanced damages were not warranted; validity of patent was "close case." 35 U.S.C.A. § 284.

44. Patents ⇒325.11(3)

Patent infringement case was not exceptional, and thus prevailing plaintiff was not entitled to award of attorney fees, absent clear and convincing evidence of willful infringement, inequitable conduct before Patent Office, or misconduct during litigation. 35 U.S.C.A. § 285.

45. Patents ⇒317

Court has broad discretion in deciding whether to grant injunction, and in determining scope of injunction, upon finding of patent infringement.

46. Patents ⇒317

That injunction might put patent infringer out of business does not justify denial of injunction.

Edward M. McNally, and Richard D. Kirk of Morris, James, Hitchens & Williams, Wilmington, Delaware, for plaintiffs. Of Counsel: Marc R. Labgold of Long, Aldridge & Norman, Washington, D.C., and Arthur I. Neustadt, Jeffrey B. McIntrye, Ron Myers of Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Arlington, Virginia.

Rudolph E. Hutz, N. Richard Powers, and Richard D. Levin of Connolly, Bove, Lodge & Hutz, Wilmington, Delaware, for defendant.

OPINION

ROBINSON, District Judge.

I. INTRODUCTION

Plaintiffs Biacore, AB and Biacore, Inc. (collectively "Biacore") filed this suit pursuant to 35 U.S.C. § 271 against defendant Thermo Bioanalysis Corporation ("Thermo") on May 29, 1997, seeking damages (lost profit damages) and an injunction for alleged infringement of a patent that is directed to a matrix coating suitable for use in a biosensor. (D.I.1) Specifically, Biacore charges that Thermo willfully infringed U.S. Patent No. 5,436,161 (the "'161 patent") entitled "Matrix Coating for Sensing Surfaces Capable of Selective Biomolecular Interactions, To Be Used in Biosensor Systems," issued July 25, 1995.[1] (D.I.1) Biacore also alleges that Thermo is inducing infringement of the patent-in-suit.

Thermo denies infringement and has counterclaimed for a declaratory judgment of invalidity and noninfringement of the '161 patent. Thermo challenges the validity of the '161 patent under 35 U.S.C. §§ 102 ("anticipation"), 103 ("obviousness"), and 112 ("written description"). Specifically, Thermo charges that: (1) the patented invention was described in a printed, prior art publication before its development by the patentee (§ 102); (2) the differences between the patented invention and the prior art are such that the claims would have been obvious to one of ordinary skill in the pertinent art (§ 103); and (3) the subject matter of the '161 patent is not disclosed in sufficient detail in the written description of the grandparent application (§ 112).[2]

The court has jurisdiction over this matter pursuant to 28 U.S.C. § 1338(a).

The parties tried this matter to the court from October 26, 1998 to November 2, 1998. Despite having identified in the pre-trial order claims 1–5, 9–11, and 15 as allegedly infringed by Thermo (D.I.96), "for purposes of trial" Biacore reduced the number of claims, asserting only claims 4 and 5. (D.I. 103 at 4) The following constitutes the court's findings of fact and conclusions of law pursuant to Fed.R.Civ.P. 52(a).

II. FINDINGS OF FACT

A. The Parties

1. Biacore, AB is a Swedish corporation with its principal place of business in Uppsala, Sweden. (D.I. 103 at 80; D.I. 1, ¶ 2) Prior to October 1996, Biacore, AB was a subsidiary of the Swedish company Pharmacia AB, operating under the name Pharmacia Biosensor, AB. (D.I. 103 at 78–79) In 1996, Pharmacia AB merged with UpJohn Pharmaceuticals and Biacore, AB was spun off. (D.I. 103 at 78–79) Biacore, AB's business is totally dedicated to the development, manufacturing, and marketing of affinity biosensors. (D.I. 103 at 80) Since 1990, it has sold its optical biosensor systems in the United States under the trade name BIAcore™. Biacore, AB is the owner of the '161 patent. (D.I. 96 at 2)

2. Biacore, Inc. is a Delaware corporation with its principal place of business in Piscataway, New Jersey. (D.I.1, ¶ 2) It is the U.S. subsidiary of Biacore, AB and is responsible for the marketing and selling of BIAcore™ optical biosensors in the United States. (D.I. 103 at 79) The BIAcore™ biosensors sold by Biacore, Inc.

1. The '161 patent is a continuation of Serial No. 058,265, filed May 10, 1993, abandoned, which was a continuation of Serial No. 681,-531, filed November 9, 1989 as PCT/EP89/00642, now U.S. Patent No. 5,242,828 (the "'828 patent"), issued September 7, 1993. *See* discussion *infra* Part II.D.

2. Thermo argues, with respect to the written description requirement, that the claims of the '161 patent contain new matter not adequately supported in the grandparent application on which the '161 patent relies for priority. Consistent with this argument, Thermo contends that the claims are entitled only to a filing date of May 10, 1993, the date they were initially presented to the Patent and Trademark Office ("PTO"). *See* discussion *infra* Part III.C.3.

are manufactured in Biac
ties in Uppsala, Sweden.

3. Thermo is a Delaw
with its principal place of b
Fe, New Mexico.[3] (D.I.1,
Thermo has marketed anc
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B. The Field of the In

4. **Biosensors.** The su
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(D.I. 104 at 266) Generally

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receptor. (D.I. 103 at 75)
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3. Thermo is a majority ov
Thermo Instrument which,
sidiary of Thermo Electron.

4. Prior to 1996, Affinity S
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In 1996, Fisons transferre
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RIES

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OF FACT

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May 10, 1993, the date they
resented to the Patent and
ce ("PTO"). *See* discussion

are manufactured in Biacore, AB's facilities in Uppsala, Sweden. (D.I. 103 at 80)

3. Thermo is a Delaware corporation with its principal place of business in Santa Fe, New Mexico.[3] (D.I.1, ¶ 3) Since 1994, Thermo has marketed and sold its optical biosensor systems in the United States under the trade name IAsys ™ through its Affinity Sensors[4] division. (D.I. 105 at 413–14)

B. The Field of the Invention

4. **Biosensors.** The subject matter of the '161 patent relates to "the field of biosensors." (Plaintiffs' Exhibit ("PX") 1, col. 1, lns. 15–16) A biosensor is

> an analytical device comprising a biological or biologically derived sensing element which is either intimately associated with or integrated within a physical chemical transducer where the transducer may be, for example, optical, electrochemical, piezoelectric, thermoelectric or magnetic.

(D.I. 104 at 266) Generally,

> [t]he usual aim [of a biosensor] is to produce a digital electronic signal which is proportional to the concentration of a specific chemical or set of chemicals.

(Defendant's Exhibit ("DX") 574 at 3) Biosensors are employed in biomolecular interaction analysis, i.e., the study and characterization of the interactions between biologically active molecules. (D.I. 103 at 74–75) For example, in the pharmaceutical industry, biosensors are used to study the binding of a novel drug to the targeted receptor. (D.I. 103 at 75) Biosensors also are employed in the fermentation and bioprocessing, petro- and agrochemical, and pollution industries. (DX 513 at 19–20)

5. A biosensor is composed of two essential elements: (1) a biorecognition system and (2) a transducer. (PX 1, col. 1, lns. 23–27; DX 513 at 20) In general, biosensors function by first immobilizing on a surface within the instrument ligands or receptors (e.g., whole cells, enzymes, lectins, antibodies, or receptor proteins) that are able to recognize target molecules (analytes[5]) over a host of other biomolecules. (D.I. 103 at 183; D.I. 104 at 219–20; DX 513 at 20) The bound ligands then are contacted with a solution or suspension containing analytes having specific recognition sites such that they will bind to the ligands. (D.I. 104 at 218–20) Generally speaking, the binding of an analyte to a ligand (i.e., the biological recognition event) results in a change in one or more parameters associated with the interaction. (DX 513 at 22) The transducer element of the biosensor functions to respond to the products of the biological recognition event,[6] converting the physio-chemical signal into a signal (e.g., an electrical output) that can be either visualized or processed in some fashion, e.g., via a computer. (D.I. 104 at 267; DX 513 at 22)

6. Biosensors employ a number of different types of transduction technologies. These technologies include thermister, electrochemical, potentiometric, optical, piezoelectric crystal, and amperometric transduction. (DX 574 at 3–4; DX 960; D.I. 106 at 759–60) Particularly relevant to the case at bar, optical biosensors employ an optical transducer that "detect[s] the change which is caused in the optical properties of a surface layer due to the interac-

3. Thermo is a majority owned subsidiary of Thermo Instrument which, in turn, is a subsidiary of Thermo Electron.

4. Prior to 1996, Affinity Sensors was owned by Fisons and operated under the name Applied Sensors Technology. (D.I. 105 at 414) In 1996, Fisons transferred the Affinity Sensors business to Thermo. (D.I. 105 at 414)

5. An analyte is "[t]he ion or compound that is being measured (determined) in a given analytical procedure." *Dictionary of Biochemistry and Molecular Biology* 26 (2d ed.1989) (hereinafter *Dictionary of Biochemistry*) . .

6. There are two broad subclasses of biological recognition events: catalytic, where there is some chemical conversion, and affinity, where only a binding event takes place. (D.I. 104 at 268)

tion of the receptor with the surrounding medium." (PX 1, col. 1, lns. 28–31; D.I. 104 at 267) One type of optical biosensor, an evanescent wave optical biosensor, exploits the energy that is propagated beyond a reflecting surface, i.e., the evanescent wave.[7] These biosensors "bring[ ] about or effect[ ] changes in the reflecting light as a result of interacting with the evanescent field," i.e., by "taking advantage of the change in refractive index causing differences in the light signal." (D.I. 104 at 267–68)

7. One type of evanescent wave technology relies on the phenomenon of surface plasmon resonance ("SPR"). SPR "is a quantum optical-electrical phenomenon that arises from the interaction of light with a suitable metal or semiconductor surface." (D.I. 27, Ex. K at 516) Under certain conditions, the photon's energy is transferred to plasmons on the surface of the metal or semiconductor. (D.I. 27, Ex. K at 516) The wavelength that excites the plasmons, the resonance wavelength, can be calculated by measuring the amount of light reflected from the surface. (D.I. 27, Ex. K at 516) The resonance wavelength is determined by the interaction between the plasmon's electric field and the matter within the field; thus, any change in the composition of the matter alters the resonance wavelength. (D.I. 27, Ex. K at 516–17) The magnitude of the change in the resonance wavelength is directly proportional to the change in composition of the surface. (D.I. 27, Ex. K at 516–17) As a result, SPR can be "exploited as a direct optical sensing technique that allows the real-time measurement of interfacial refractive index (dielectric) changes ... made at suitable metal or dielectric surfaces ... without the use of labels or probes." (D.I. 27, Ex. K at 518) SPR optical biosensor technology, therefore, is a method whereby "changes in the refractive index in a layer close to a thin metal film are detected by consequential changes in the intensity of a reflected light beam." (PX 1, col. 1, lns. 44–47) Biacore's biosensors employ SPR technology.

8. Another type of evanescent wave system technology employs "an integrated optical chip called the resonant mirror (RM)," which "comprises a glass prism with the top surface coated with a low refractive index silica spacer layer which is in turn coated with a thinner high refractive index monomode wave-guide of titania, hafnia or silicon nitride. This is then coated with the bioselective layer." (D.I. 27, Ex. K at 519) In operation, a laser light directed at the prism "is repeatedly swept through an arc of specific angles," generating, *inter alia*, an evanescent wave at the waveguide surface that penetrates into the sample. (D.I. 27, Ex. K at 519–20) "This wave detects surface binding events by detecting the changes in the refractive index which in turn change the resonance angle that is tracked by diode arrays." (D.I. 27, Ex. K at 520) Thermo's biosensors employ a resonant mirror.

9. **Hydrogel.** The '161 patent specifically discloses a matrix coating that is comprised of a hydrogel. A gel, of which a hydrogel is a type, is "a solid colloidal dispersion consisting of a network of particles and a solvent that is immobilized in this network." *Dictionary of Biochemistry* 192. A hydrogel is a material that imbibes or absorbs a large amount of water, a common example of which is gelatin. (D.I. 106 at 760–61) Because hydrogels are composed mostly of water, thus resembling the environment in which most biomolecules are found, they have good biocompatibility, i.e., bound biomolecules are more likely to be stable. (D.I. 106 at 761–62) Polysaccharide[8] hydrogels and water-swellable polymer hydrogels are conven-

7. An evanescent wave is an "electromagnetic field that decays exponentially away from the surface but propagates along the surface." (D.I. 27, Ex. K at 515)

8. A polysaccharide is a polymeric material composed of more than ten monosaccharides (sugars) linked by glycosidic bonds. *See Dictionary of Biochemistry* 374.

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tional ligand immobilization reagents. (DX 574 at 2)

10. **Ligand Immobilization.** In the context of the technology at issue, a ligand is a molecule that binds to a macromolecule. *See Dictionary of Biochemistry* 273. Ligand immobilization is a method of fixing a biomolecule to a surface in some particular orientation. (D.I. 106 at 752–53) This procedure has long been employed in various types of chromatography. (D.I. 104 at 242–44) Although there are many ways by which to bind ligands to a surface, with respect to the technology at issue, they are immobilized via covalent bonding[9] with reactive groups in the hydrogel matrix. (D.I. 106 at 752–53) In addition to biosensor technology, ligand immobilization is used in a wide variety of fields, including diagnostic assays, enzyme immobilization, and protein purification. (D.I. 106 at 753)

11. **Activation.** According to the '161 patent, the hydrogel is activated to contain two types of chemical groups: charged groups capable of concentrating oppositely-charged biomolecules and reactive groups capable of covalently binding the concentrated biomolecules. In the context of ligand immobilization, "activated" refers to the state of reactivity required to covalently bind another biomolecule under conditions that would not result in alteration of the biomolecule itself, with the exception of that alteration necessary to allow for the covalent binding. (D.I. 106 at 762) In contrast to activated groups, which are able to react with and bind a biomolecule under the mild conditions necessary for biomolecule immobilization, reactive groups react under reasonable, or "normal," conditions. (D.I. 106 at 766) Charged groups, as that term is understood in the art of ligand immobilization, are groups containing either a positive or negative charge. (D.I. 106 at 764) They function to concentrate or attract oppositely-charged biomolecules. (D.I. 106 at 764) In general, the term "charged groups" describes the use of an electrostatic concentration. (D.I. 107 at 867)

12. In the context of the '161 patent, the ligands are concentrated into the hydrogel matrix via the electrostatic charge created by the presence of oppositely-charged groups incorporated into the hydrogel. (D.I. 107 at 867–68) The reactive groups in the hydrogel then act to covalently bind the concentrated ligands to the hydrogel in an orientation that preserves the ligands' affinity[10] function. (D.I. 107 at 868) As a result, the immobilized ligands are able to attract the analytes from the solution. (D.I. 107 at 868)

C. The Technology Developed by the Biacore Researchers

13. As of 1983, a number of obstacles faced researchers attempting to develop a functional biosensor. These problems had to do with capacity, activity, and nonspecific binding. (D.I. 103 at 188–90; D.I. 104 at 271–72) With regard to capacity, the two-dimensional (i.e., planar) surfaces employed in the prototypical biosensor limited the amount of available surface area. (D.I. 103 at 188–90; D.I. 104 at 271–72) Even if the ligands were tightly packed on the surface, there was insufficient ligand immobilization to yield a signal that would be of use for biosensor purposes. (D.I. 103 at 188–90; D.I. 104 at 271–72) The capacity problem was exacerbated by the activity problem, which was two-fold. (D.I. 103 at 188–90; D.I. 104 at 271–72) Specifically, the ligands would bind to the surface in an orientation that would prevent them from interacting with the ana-

9. A covalent bond is "formed between two atoms and consist[s] of one or more shared pairs of electrons such that one electron in a pair is donated by each of the two bonded atoms." *Dictionary of Biochemistry* 105. A covalent bond "creates an integral molecule." (D.I. 106 at 753)

10. In the context of the technology at issue, affinity is the capacity of a ligand to bind the desired analyte. *See Dictionary of Biochemistry* 13.

lytes. (D.I. 103 at 188–90; D.I. 104 at 271–72) Moreover, direct adsorption often would cause the ligands to denature, i.e., breakdown, thereby losing their ability to function. (D.I. 103 at 188–90; D.I. 104 at 271–72) Finally, nonspecific binding, i.e., unwanted binding events at the surface, would contribute to the signal coming from the biosensor unit and thereby confound the data. (D.I. 103 at 188–90; D.I. 104 at 271–72) In addition, a problem specific to evanescent wave optical biosensors concerned maximizing the biomolecular interactions throughout the available detection field, which extends a few hundred nanometers above the sensor surface. (D.I. 104 at 271; PX 33 at 101020)

14. In 1984, Pharmacia, AB created a division, Pharmacia Biosensor, AB ("Pharmacia"), solely for the purpose of developing a functional affinity-based biosensor for the study of biomolecular interaction. (D.I. 103 at 71–72; PX 360 at BIA 003080–81) Interest in the field had been stimulated by the publication in 1983 of an article by researchers at Linköping University in Sweden demonstrating, for the first time, the use of SPR for biosensing applications. (D.I. 104 at 269–70, 275–74) Competition in the field was high. (D.I. 104 at 275) Initially, the Pharmacia researchers employed functioning coupling reagents and methods that were being used at that time for affinity chromatography and enzyme immobilization. (D.I. 104 at 247–48) They worked with two-dimensional silicon surfaces, immobilizing ligands via either silanization of the surface or direct adsorption. (D.I. 103 at 185–87) Neither method, however, yielded a workable or usable biosensor as the aforementioned salient problems persisted. (D.I. 103 at 187)

15. By September 1985, the Pharmacia researchers had introduced hydrogels to the surface in an attempt to decrease, or obviate altogether, the incidence of nonspecific binding. (D.I. 103 at 190; D.I. 104 at 274) At that time, it was known that hydrogels, because they are highly watersolvated, form a biocompatible surface. (D.I. 104 at 274; D.I. 106 at 761–62) The Pharmacia researchers believed that the attachment of a hydrogel would hamper the ability of undesired biomolecules (i.e., biomolecules other than the analytes) to contact the surface, thereby minimizing nonspecific binding, while at the same time displaying the required ligand. (D.I. 103 at 190–91; D.I. 104 at 275) In addition, the introduction of a hydrogel would create a three-dimensional matrix thus increasing capacity and exploiting the evanescent wave phenomenon to the greatest extent. (D.I. 103 at 191; D.I. 104 at 267–68, 273–74) Finally, the researchers postulated that attachment of ligands to a fluid hydrogel structure, rather than a planar surface, would not only increase accessibility, resulting in a commensurate increase in activity, but would also decrease the incidence of ligand denaturation. (D.I. 103 at 191; D.I. 104 at 274)

16. The first hydrogel employed by the Pharmacia researchers was dextran. (D.I. 103 at 192) At that time dextran, a naturally occurring polysaccharide, was being used in chromatography procedures as a matrix for the binding of biomolecules. (D.I. 104 at 244; PX 1 col. 6, ln. 6) The researchers selected dextran because it was a biocompatible and, ostensibly, inert material. (D.I. 103 at 192; D.I. 104 at 233; D.I. 106 at 762) Moreover, it was readily available in different grades from Pharmacia. (D.I. 103 at 192; D.I. 104 at 232–33) The fact that dextran was thought to be inert was important to the Pharmacia researchers, who wished to avoid any nonspecific binding caused by charged interactions between the nonanalyte biomolecules in the solution and charged groups on the biosensor surface. (D.I. 103 at 192)

17. Although dextran's inert nature was beneficial with respect to reducing nonspecific binding, it was a disadvantage with respect to immobilizing ligands. (D.I. 103 at 192; PX 489 at 289) Therefore, the Pharmacia researchers sought to modify the dextran by introducing reactive groups that could covalently bind ligands

into the dextran. (D.I. 103 at 192–94) The scientists experimented with a variety of conventional reagents, including allyglycidylether, cyanodimethypyridin, carbonyldiimidazole, and tresyl chloride.[11] (D.I. 103 at 192–94) In each instance, however, the modified dextran failed to yield a matrix suitable for use in a biosensor, i.e., the signal produced was not "good enough" because an insufficient amount of active ligand was bound. (D.I. 103 at 193)

18. In the summer of 1986, having failed to produce a workable matrix, the Pharmacia researchers began exploring the possibility of employing SPR technology techniques that had been developed elsewhere in the company for use in non-biosensor applications. (D.I. 103 at 195) Specifically, the researchers began to experiment with charged hydrogel surfaces, conjecturing that these surfaces would interact with ligands by electrostatic attraction.[12] (D.I. 103 at 195) The results of the experiments demonstrated that, by using a dextran hydrogel matrix possessing both charged and reactive groups, a dramatic increase in capacity (over 1000%) could be achieved, even at reduced concentrations of ligands. (D.I. 103 at 195–96) The activated hydrogel matrix employed in these experiments was attached to a silicon oxide surface via well-known silanization procedures. (D.I. 103 at 196–97) The resulting sensing element was suitable for use in a biosensor.

D. The '161 Patent Application

19. **The PCT Application.** On November 9, 1989, three researchers from Pharmacia, Jan Bergström, Stefan Löfås, and Bo Johnsson, filed Patent Cooperation Treaty application PCT/SE89/00642 ("the PCT") entitled "Sensing Surfaces Capable of Selective Biomolecular Interactions, To Be Used in Biosensor Systems." (Joint Exhibit ("JX") 1) The application claimed priority from Swedish patent application 8804073 filed on November 10, 1988. (JX 1 at BIA 001545) The PCT was published on May 17, 1990. (JX 1 at BIA 001545)

20. The PCT is directed to

> [m]ethods for the production, on metal surfaces, of surface layers which are capable of selective biomolecular interactions; sensing surfaces produced by means of these methods; and the use thereof in biosensors, especially in surface plasmon resonance systems.

(JX 1 at BIA 001545) The invention also discloses

> activated surfaces for coupling a desired ligand; surfaces containing bound ligand; and the use of such surfaces in biosensors.

(JX 1 at BIA 001547) The PCT teaches a barrier monolayer of an "organic molecule X–R–Y" between the metallic surface of an SPR system and the desired ligands in order to bind the ligands and protect the metal surface. (JX 1) In addition, an optional embodiment discloses a matrix comprised of a hydrogel coupled to the X–R–Y monolayer by which ligands suitable for the target analytes can be immobilized. (JX 1 at BIA 001553–54) Although acknowledging that there exist methods for attaching a hydrogel directly to a surface, the specification of the PCT contends that these methods "ha[ve] a number of obvious drawbacks;" it also recognizes that these "problems" can be "solved at least in part" by known procedures. (JX 1 at BIA 001549–50)

21. The PCT contains 14 claims. Claim 1 of the PCT is a generic claim drawn to a "sensing surface" for use in a

11. Dextran modified with these agents would contain only reactive groups.

12. Previously, the Pharmacia researchers had avoided incorporating charged groups into the hydrogel matrix since it was well-known in the art of affinity chromatography that the presence of charged groups increases the incidence of nonspecific binding, a condition that was to be avoided in affinity-based systems. (D.I. 103 at 192)

biosensor. (JX 1 at BIA 001569) Claim 1 discloses a

> [s]ensing surface to be used in biosensors, characterized by consisting of a film of a free electron metal selected from the group consisting of copper, silver, aluminum and gold and having one of its faces coated with a densely packed monolayer of an organic molecule X–R–Y . . .

(JX 1 at BIA 001569) Claim 1 is the only independent claim; all the other claims, which are drawn to specific variations of the sensing surface described in claim 1, contain the limitations found in claim 1.

22. Claim 2 of the PCT discloses an optional embodiment:

> [A s]ensing surface according to claim 1, characterized by containing a biocompatible porous matrix which is bound to the monolayer X–R–Y and via which a desired ligand can be bound.

(JX 1 at BIA 001569) Claims 3–13, which are drawn to specific variations of the sensing surface described in claim 2, contain the limitations set forth in claim 2.[13]

23. **The U.S. Patent Applications. The '828 patent.** The same inventors who filed the PCT application filed the United States counterpart application, Serial No. 681,531, and a Preliminary Amendment with the PTO on May 10, 1991. (D.I. 96 at 2; PX 5) As with the PCT, the inventors claimed a priority filing date of November 10, 1988 based upon the Swedish patent application.

24. The claims of the U.S. counterpart patent initially were rejected, *inter alia*, as obvious over the prior art. In their response to the rejection, the applicants stated that

> [t]he basic concept of the present invention resides in providing a biosensor sensing surface, in the form of a free electron metal film, with a barrier layer comprising monomeric organic molecules which, through self-association, form a well-defined, dense and stable monolayer.

(PX 5) The applicants distinguished the prior art based on the presence in the invention of the barrier (i.e., the densely packed monolayer of organic monomeric molecules) alone or in combination with "a porous matrix":

> No such barrier layer, nor its combination with a porous matrix such as a hydrogel, is disclosed or suggested by the cited references, either individually or in combination.

(PX 5) According to the applicants, the prior art references relied upon by the patent examiner disclose polymeric coatings. The applicants argued that the polymers of these coatings are either not as efficiently densely-packed as is the monolayer disclosed in the invention, thus providing less protection against corrosion and nonspecific binding, or are not bound to the surface in a manner so as to provide stability, uniformity, and durability. (PX 5) The applicants requested withdrawal of the rejection, concluding that

> the cited prior art does not disclose or suggest a sensing surface comprising a metal film coated with a densely packed monolayer of organic molecules X–R–Y as defined in claim 1, nor does it disclose or suggest such a barrier layer supporting a three-dimensional porous matrix, preferably a hydrogel, onto which ligands and analytes may be bound.

(PX 5)

25. On September 7, 1993, the U.S. counterpart application was issued as U.S. Patent 5,242,828 (the "'828 patent"). (PX 4) The specification of the '828 patent is essentially the same as that of the PCT. The claimed invention relates to

13. Claim 14 depends solely from claim 1, providing as follows:

> [A s]ensing surface according to claim 1, characterized by containing a ligand which is bound to the monolayer X–R–Y.

(JX 1 at BIA 001571)

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the '828 patent also claims
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packed monolayer of an or
X–R–Y coated on said sec
face of said film." (PX 4,
63)

27. The sensing surfac
described in the '828 pater

14. Independent claim 26 of
also discloses a "sensing su
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Said surface comprises

> a film, having two faces,
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> copper, silver, aluminum
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the field of biosensors and is more specifically concerned with methods for providing metal surfaces with surface layers capable of selective biomolecular interactions. The invention also comprises activated surfaces for coupling a desired ligand; surfaces containing bound ligand and the use of such surfaces in biosensors.

(PX 4, col. 1, lns. 8–14; *see also* col. 8, lns. 16–21: "The invention relating to (i) the aforesaid methods for providing metal surfaces with surface layers capable of selective biomolecular interactions, to be used in biosensor systems ....") The examples set forth in the specification of the '828 patent are drawn to SPR technology and demonstrate a hydrogel attached to a metal surface via an X–R–Y monolayer. (PX 4; D.I. 104 at 316) The specification does not describe a hydrogel attached to a non-metal surface other than by reference to further patent applications. (D.I. 104 at 232, 316)

26. Whereas the PCT contains 14 claims, the '828 patent contains 27 claims. (PX 4) Besides claiming the sensing surface described and claimed in the PCT, the '828 patent also claims a "sensing element suitable for use in a biosensor" comprising a substrate, "a film of free electron metal ... having a first and second major surface, said first major surface being in contact with the substrate," and "a densely packed monolayer of an organic molecule X–R–Y coated on said second major surface of said film." (PX 4, col. 14, lns. 38–63)

27. The sensing surface claimed and described in the '828 patent essentially is the same as that claimed in the PCT. Claim 1 of the '828 patent discloses

> 1. A sensing surface suitable for use in a biosensor, comprising:
>
> a film, having two faces, of a free electron metal selected from the group consisting of copper, silver, aluminum and gold; and
>
> a densely packed monolayer of an organic molecule X–R–Y coated on one of the faces of said film where X is a group selected from the group consisting of ....

(PX 4, col. 13, lns. 6–27) Whereas claims 2–16 of the '828 patent depend in part from claim 1, claims 17–21 depend solely from claim 1.[14]

28. As in the PCT, claim 2 of the '828 patent describes an optional embodiment:

> 2. The sensing surface according to claim 1, which contains a biocompatible porous matrix which is bound to the densely packed monolayer X–R–Y and via which a desired ligand can be bound.

(PX 4, col. 13, lns. 28–31) Claims 3–16 are drawn to variations of the sensing surface disclosed in claim 2 and contain all the limitations found in claim 2.

29. **The '161 patent.** On May 10, 1993, the inventors of the '828 patent filed a continuation application, Serial No. 058,265 (the "'265 application") and a Preliminary Amendment. (PX 3) Claim 1, as set forth in the Preliminary Amendment, disclosed

> [a] sensing surface suitable for use in a biosensor, comprising a hydrogel which is bound to a surface and via which a desired ligand can be bound, which hydrogel is activated to contain (i) charged

14. Independent claim 26 of the '828 patent also discloses a "sensing surface suitable for use in a biosensor." (PX 4, col. 15, ln. 4) Said surface comprises

> a film, having two faces, of a free electron metal selected from the group consisting of copper, silver, aluminum and gold; and a monolayer of an organic molecule X–R–Y coated on one of the faces of said film where X is a group selected from the group consisting of ....

(PX 4, col. 15, ln. 6—col. 16, ln. 10) Claim 27 depends from claim 26 and provides as follows:

> The sensing surface of claim 26, wherein said monolayer forms an efficient barrier layer which is stable upon storage and which protects said film from chemical corrosion.

(PX 4, col. 16, lns. 11–14)

> groups for bringing about a concentration of biomolecules carrying an opposite charge to that of said charged groups, and (ii) reactive groups for covalently binding said biomolecules concentrated to said sensing surface.

(PX 3 at 68) In contrast to the claims of the '828 patent, the claims of the '265 application did not recite a densely packed monolayer of organic monomeric molecules forming a barrier on a metal surface.

30. On November 8, 1993, during the prosecution of the '265 application, the claims were rejected by the patent examiner for obviousness-type double patenting over the '828 patent. (PX 3, Tab 6) In response to this rejection, on April 20, 1994, the inventors filed a terminal disclaimer, disclaiming the '265 application beyond the expiration date of the '828 patent. (PX 3, Tab 8)

31. The claims were also rejected as obvious in light of the prior art, specifically European Patent Application Publication No. 0 226 470 (the " '470 patent") in combination with other prior art references. (PX 3, Tab 6) In this regard, the patent examiner opined that the prior art already disclosed the use of an activated hydrogel on a surface and that such "an 'activated' hydrogel would inherently provide for the claimed features of charged and reactive groups." (PX 3, Tab 6 at BIA 000116) In response to this rejection, the applicants distinguished the prior art, individually and in combination, asserting that

> none of the cited references (1) discloses or suggests the concept of combining charged and reactive groups; (2) contains any example where the hydrogel has been provided with both charged and reactive groups; or (3) discloses or suggests that an activated hydrogel would have a concentrating effect on biomolecules.

(PX 3, Tab 7 at BIA 000153)

32. Although the claims of the '265 application ultimately were allowed, the application subsequently was abandoned, and on July 22, 1994, the inventors filed another continuation application, Serial No. 279,089. (PX 3, Tabs 11, 12, and 13) The claims of this application were initially rejected by the patent examiner, *inter alia*, "as being indefinite for failing to particularly point and distinctly claim the subject matter which applicant regards as the invention." (PX 3, Tab 15 at BIA 000333) The examiner noted, however, that the subject matter of the application was allowable:

> The prior art discloses the use of charged species to concentrate biomolecules to an area and the use of charged species to improve binding capabilities, however fails to disclose the use of a hydrogel, bound to a substrate, that has charged groups for concentrating biomolecules and uncharged groups ("reactive groups") for binding an analyte.

(PX 3, Tab 15 at BIA 000334) Following revision of the application in accordance with the examiner's comments, this application issued as the '161 patent on July 25, 1995.[15] (PX 3, Tab 17)

E. The '161 Patent

33. **The abstract and specification.** The abstract describes the invention claimed in the '161 patent as follows:

> A matrix coating suitable for use in a biosensor is provided. This matrix coating comprises a hydrogel bound to a surface and via which a desired ligand can be bound. This hydrogel is activated to contain charged groups for bringing about the concentration of biomolecules carrying an opposite charge to that of said charged groups, and reactive groups for covalently binding the biomolecules concentrated to the matrix coating.

(PX 1, Abstract)

34. The specification of the '161 patent, which is essentially the same as that of

15. On February 4, 1998, Biacore filed a terminal disclaimer in the PTO disclaiming the '161 patent beyond the expiration date of the '828 patent. (DX 578) The PTO granted the disclaimer on September 8, 1998. (PX 431)

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994, the inventors filed anoth-
n application, Serial No. 279,-
Tabs 11, 12, and 13) The
application were initially re-
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(DX 578) The PTO granted
September 8, 1998. (PX

the '828 patent, includes the following field of the invention:

> The present invention relates to the field of biosensors and is more specifically concerned with methods for providing metal surfaces with surface layers capable of selective biomolecular interactions. The present invention also comprises activated surfaces for coupling a desired ligand; surfaces containing bound ligand; and the use of such surfaces in biosensors.

(PX 1, col. 1, lns. 15–21) The invention claimed is described as

> [a] generally useful sensing surface for biosensor systems, especially SPR, ... fulfil[ling] the following desiderata:
>
> ... [C]hemically resistant to the media employed.
>
> ... [C]ompatible with proteins and other biomolecules and ... not interact[ing] with any molecules other than those desired.
>
> ... [C]apable of providing for covalent binding of such a large number of ligands as is required for a general applicability of this technique to a variety of analytical problems.
>
> ... [P]rovid[ing] a tridimensional matrix for the sample solution for binding the target molecules therein. In this manner a greater part of the volume influencing the resonance effect, by way of its refractive index, will be utilized as compared to cases where a two-dimensional surface would be used.

(PX 1, col. 3, lns. 19–39)

35. The specification indicates that the scope of applicability of the claimed invention extends beyond the field of biosensor technology. Specifically, it is noted that

- [f]urther scope of the applicability of the present invention will become apparent from the detailed description and drawings provided [herein]. (col.3, lns.43–45)
- [t]his type of surface modification can be utilized also in other fields of technology where a specific, or alternatively, a low non-specific, interaction is required between a surface on one hand and proteins or other biomolecules on the other hand. Examples that may be mentioned are parts of chromatographic systems for biomolecule separations .... It would also be possible to construct capillary-type chromatographic columns in conformity with these principles. Furthermore, it is evident that a surface structure may be modified so as to acquire biocompatibility, for use in environments of the "in vivo" type. Depending on the particular field of use contemplated, the actual choice of, for example, the hydrogel, can be made such that undesired interactions are minimized. To those skilled in the art, a number of additional fields of use will be readily obvious, along the lines of the aforesaid examples. (col.6, lns.20–38)
- [i]t will be readily evident that ion exchanging groups, metal chelating groups and various types of receptors for biological molecules—such as are known from conventional liquid chromatographic procedures—may be employed for the construction of systems which are suitable for selection purposes even in complex measuring systems. (col.7, lns.40–48)

36. **The claims.** The '161 patent contains 15 claims. Claim 1 is a generic claim, drawn to a "matrix coating suitable for use in a biosensor." Claims 2–4 are drawn specifically to particular modifications of the matrix described in claim 1. Claim 15 is drawn to a "sensing element suitable for use in a biosensor." Claims 1 and 15 are the only independent claims; claims 2–14 depend, at least in part, on claim 1. Biacore alleges that Thermo has infringed claims 4 and 5 of the '161 patent. Thermo seeks a declaratory judgment of invalidity with respect to claims 1–5, 9–11, and 15.

37. Claim 1 reads:

> 1. A matrix coating suitable for use in a biosensor, comprising a hydrogel which is bound to a surface and via which a desired ligand can be bound, which hydrogel is activated to contain (i) charged groups for bringing about a concentration of biomolecules carrying an opposite charge to that of said charged groups, and (ii) reactive groups for covalently binding said biomolecules concentrated to said matrix coating.

(PX 1, col. 12, ln. 63—col. 13, ln. 2)

38. Claim 1 is directed to a matrix coating "suitable for use in a biosensor." As defined in the patent, a biosensor is

> a unique combination of a receptor for molecular recognition, for example a selective layer with immobilized antibodies, and a transducer for transmitting the interaction information to processable signals.

(PX 1, col. 1, lns. 23–27) This broad definition comports with the definitions found in the literature relevant to biosensor technology.

39. The disclosed matrix coating is further described as comprising a "hydrogel which is bound to the surface." The patent defines hydrogel by reference to Merrill et al., *Hydrogels for Blood Contact* (1986). (PX 1, col. 5, lns. 49–52) According to Merrill, a hydrogel

> presents a surface layer of bound molecules which by reason of their chemical nature hold a large fraction of water, in which the molecules are predominantly in an amorphous, water-solvated state, and in which the thickness of the layer is of the order of 30 Å minimum up to any indefinitely higher limit.

(JX 3 at 2; PX 1, col. 5, lns. 49–52; D.I. 103 at 199; D.I. 106 760–61) Dr. William H. Scouten, Thermo's expert witness, opined that this definition "does not differ substantially from what a person of ordinary skill in the art would understand the plain meaning of the word 'hydrogel'" to be. (D.I. 107 at 858–59) The means by which the hydrogel is bound to the surface is not limited in the patent to any specific binding chemistry; thus, any form of contact, covalent, physical, or adhesive, is sufficient. (D.I. 104 at 231–32, 294; D.I. 107 at 859–60) Nor is the type of surface to which the hydrogel is bound limited despite the fact that the examples set forth in the specification refer only to metallic surfaces.[16] (D.I. 103 at 205–07; D.I. 104 at 246–47, 251–52, 287–92; D.I. 106 at 766; D.I. 107 at 858)

40. The hydrogel disclosed in claim 1 must be able to bind the desired ligands. (*see also* PX 1, col. 1, lns. 48–49: "[A] sensing surface composed of ... 'ligands.'") According to the patent, ligands, or receptors, are "molecules or molecular structures which interact selectively with one or more biomolecules." (PX 1, col. 1, lns. 48–51) Within the context of claim 1, ligand is used in the same manner as that term is employed in the field of affinity chromatography. (D.I. 107 at 863) The patent does not specifically limit the means by which the ligands are bound to the hydrogel. (D.I. 104 at 253–54)

41. Said hydrogel is "activated to contain" two types of chemical groups. These groups are defined by their function. (D.I. 104 at 235) Specifically, the groups are: (1) charged groups for concentrating oppositely-charged biomolecules and (2) reactive groups for covalently binding the concentrated biomolecules. (PX 1, col. 12, ln. 66—col. 13, ln. 2) The patent does not specify the degree or amount of charge required with respect to the charged groups or the degree of ligand concentration required by the reactive groups. (D.I. 106 at 780, 791) Nor does the patent state the relative ratio of the two chemical groups or the chemical nature of the groups, except as that is limited by the function to be performed. (D.I. 104 at 234–35) In fact, the patent allows for the

16. Prior to trial, Thermo asserted that the claims should be limited to metal surfaces. Thermo appears, however, to have abandoned this position.

two groups to be one and
the same chemical group or
could serve both functions.
234; D.I. 106 at 777) No m
in the patent as to the pr
the charged and reactive g
onto the hydrogel. (D.I. 1

42. Dependent claims
provide as follows:

2. The matrix coating
claim 1, wherein said hyd
saccharide or a swellable
mer.

3. The matrix coating
claim 2, wherein said hyd
saccharide selected from
sisting of agarose, dextra
alginic acid, starch, and c
derivative of any of the fo

4. The matrix coating
claim 3, wherein said hy
of dextran.

5. The matrix coating
claim 4, wherein said c
and said reactive groups
are carboxyl groups, part
the form of reactive este
thiols, or reactive disu
derivatives.

* * * *

9. The matrix coating
claim 2, wherein said c
and said reactive groups
gel are carboxyl groups,
are in the form of reactive
zides, thiols, or reactive
taining derivatives.

10. The matrix coating
claim 1, wherein said c
and said reactive groups
gel are selected from the
ing of hydroxyl groups, c
amino groups, aldehyde
nyl groups, epoxy grou
groups for immobilizing a
and, optionally, a bio
bound via said groups.

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at 858–59) The means by
·gel is bound to the surface
ι the patent to any specific
ry; thus, any form of con-
hysical, or adhesive, is suf-
)4 at 231–32, 294; D.I. 107
is the type of surface to
·ogel is bound limited de-
ıat the examples set forth
tion refer only to metallic
. 103 at 205–07; D.I. 104 at
287–92; D.I. 106 at 766;

rogel disclosed in claim 1
) bind the desired ligands.
, col. 1, lns. 48–49: "[A]
e composed of ... 'li-
ording to the patent, li-
ptors, are "molecules or
tures which interact selec-
e or more biomolecules."
.s. 48–51) Within the con-
ligand is used in the same
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he hydrogel. (D.I. 104 at

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of chemical groups. These
ed by their function. (D.I.
ifically, the groups are: (1)
for concentrating opposite-
nolecules and (2) reactive
lently binding the concen-
ules. (PX 1, col. 12, ln.
2) The patent does not
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respect to the charged
legree of ligand concentra-
the reactive groups. (D.I.
Nor does the patent state
itio of the two chemical
chemical nature of the
as that is limited by the
performed. (D.I. 104 at
the patent allows for the

s, however, to have abandoned

two groups to be one and the same, i.e., the same chemical group on the hydrogel could serve both functions. (D.I. 104 at 234; D.I. 106 at 777) No mention is made in the patent as to the process whereby the charged and reactive groups are put onto the hydrogel. (D.I. 104 at 244–45)

42. Dependent claims 2–5 and 9–11 provide as follows:

> 2. The matrix coating according to claim 1, wherein said hydrogel is a polysaccharide or a swellable organic polymer.
>
> 3. The matrix coating according to claim 2, wherein said hydrogel is a polysaccharide selected from the group consisting of agarose, dextran, carrageenan, alginic acid, starch, and cellulose, and a derivative of any of the foregoing.
>
> 4. The matrix coating according to claim 3, wherein said hydrogel consists of dextran.
>
> 5. The matrix coating according to claim 4, wherein said charged groups and said reactive groups of said dextran are carboxyl groups, part of which are in the form of reactive esters, hydrazides, thiols, or reactive disulfide-containing derivatives.
>
> * * * * * *
>
> 9. The matrix coating according to claim 2, wherein said charged groups and said reactive groups of said hydrogel are carboxyl groups, part of which are in the form of reactive esters, hydrazides, thiols, or reactive disulfide-containing derivatives.
>
> 10. The matrix coating according to claim 1, wherein said charged groups and said reactive groups of said hydrogel are selected from the group consisting of hydroxyl groups, carboxyl groups, amino groups, aldehyde groups, carbonyl groups, epoxy groups, and vinyl groups for immobilizing a desired ligand, and, optionally, a biospecific ligand bound via said groups.
>
> 11. The matrix coating according to claim 1, wherein said charged groups are carboxyl groups.

(PX 1, col. 13, lns. 3–19; col. 13, ln. 31—col. 14, ln. 11)

43. Independent claim 15 is drawn to "[a] sensing element for use in a biosensor," said sensing element

> comprising:
>
> a substrate; and
>
> a matrix coating comprising a hydrogel supported on said substrate via which a desired ligand can be bound, which hydrogel has been activated to contain (i) charged groups for bringing about a concentration of biomolecules carrying an opposite charge to that of said charged groups, and (ii) reactive groups for covalently binding said biomolecules concentrated on said matrix coating.

(PX 1, col. 14, lns. 23–32) The patent does not limit the term "sensing element" to any particular type or types of element capable of detecting an analyte. In addition, the patent does not specifically limit the type of surface to be employed or the means for supporting the hydrogel on the substrate.

F. The Prior Art

44. The publications characterized by Thermo as prior art include: (1) the '470 patent published June 24, 1987; (2) an article entitled *Polysaccharide Derivatives as Coats for Nylon Tube Urease* authored by Francis N. Onyezili and Akintunde C. Onitiri and published in *Analytical Biochemistry*, Vol. 117, in 1981 (the "Onyezili reference"); (3) an article authored by Carl Fredrik Mandenius et al. entitled *Reversible and Specific Interaction of Dehydrogenases with a Coenzyme–Coated Surface Continuously Monitored with a Reflectometer* that was published in *Analytical Biochemistry*, Vol. 157, in 1986 (the "Mandenius reference"); (4) a paper authored by Dr. Scouten et al. entitled *Immobilizing Fluorescently–Labeled Albumin for Use in a Fiberoptic Bilirubin*

Monitor that was presented at the Chemically Modified Surfaces symposium in June 1987 (the "Scouten paper"); (5) a survey article authored by Dr. Scouten entitled *A Survey of Enzyme Coupling Techniques* that was published in Vol. 135 of *Methods in Enzymology, Immobilized Enzymes and Cells Part B* in 1987 (the "Scouten survey article"); (6) an article entitled *Simple Hydrazidation Method for Carboxymethyl Groups on Cross-Linked Dextran* authored by Hiroshi Akanuma and Makoto Yamasaki and published in the *Journal of Biochemistry,* Vol. 84, in 1984 (the "Akanuma reference"); (7) an article authored by Russell G. Frost et al. entitled *Covalent Immobilization of Proteins to N-Hydroxysuccinimide Ester Derivatives of Agarose—Effect of Protein Charge on Immobilization* that was published in *Biochimica et Biophysica Acta,* Vol. 670, in 1981 (the "Frost reference"); (8) an article authored by Suresh B. Shukla entitled *Preparation of an Active Ester Agarose Derivative Having a Positively Charged Spacer Arm; Enhanced Coupling to Acidic Proteins* that was published in *Affinity Chromatography and Biological Recognition* in 1983 (the "Shukla reference"); (9) an article entitled *Covalent Immobilization of Enzymes on Ionogenic Carriers* authored by V.P. Torchilin et al. and published in the *Journal of Solid-Phase Biochemistry,* Vol. 2, in 1977 (the "Torchilin reference"); (10) U.S. Patent No. 3,619,371 entitled "Production of a Polymeric Matrix Having a Biologically Active Substance Bound Thereto" issued on November 9, 1971 with a priority date of July 3, 1967 (the "Crook patent"); and (11) a 1986 brochure for Activated Affinity Supports Affi-Gel 10 and 15 by Bio-Rad Laboratories (the "Bio-Rad brochure"). All of these references are within the field of ligand immobilization. It is undisputed that these references were publicly available more than one year prior to the priority date at issue and, thus, constitute prior art. Thermo contends that four of these references, the '470 patent, the Onyezili article, the Mandenius reference, and the Scouten paper, each standing alone, anticipate the asserted claims of the '161 patent with the exception of claim 5. Alternatively, Thermo contends that the claimed invention is obvious in light of the identified prior art.

45. **The teachings of the '470 patent.**[17] The '470 patent discloses a microchemical analytic apparatus comprising a solid substrate having a surface that carries a hydrogel formed thereon and covalently bound thereto. (DX 541) The patent considers the invention's use in an electrochemical biosensor as well as its suitability for use in other types of biosensors, such as thermistors and optical biosensors. (DX 541 at Col. 3, ln. 55—col. 4, ln. 3; col. 7, lns. 2–20; D.I. 107 at 813)

46. Example 5 of the '490 patent describes a method for preparing a matrix coating comprising an acrylate hydrogel bound to a glass slide. According to the patent,

> the carboxyl groups contained within the polymer matrix may be activated by treatment with, for example, an aqueous solution Woodward's Reagent K .... The activated copolymer may then be reacted with functional groups such as antibody protein molecules, antigens, or haptens.

(DX 541, col. 8, lns. 43–49) According to Dr. Scouten, the Woodward's Reagent K, which possesses an overall neutral charge with a positive amine and a negative sul-

17. A copy of the '470 patent was provided to the PTO by the patentees during the prosecution of the '161 patent. Initially, the examiner rejected claims 15–27 of the application over the '470 patent, stating that "[i]t is believed that an 'activated' hydrogel would inherently provide for the claimed features of charged and reactive groups." (PX 2, Paper No. 6 at 6) Thermo contends that Biacore's predecessor in response to this rejection misrepresented the teaching of the '470 patent when it stated "none of the cited references ... (2) contains any example where the hydrogel has been provided with both charged and reactive groups." (PX 2, Paper No. 7 at 16)

fate group, reacts with the carboxyl groups on the polymer to form a "charged and activated reactive ester." (D.I. 106 at 792) Thus, the activated hydrogel disclosed in example 5 of the '470 patent contains charged groups, the Woodward's Reagent K sulfate groups as well as any of the original carboxyl groups that did not react, and reactive groups, the reactive esters, that "happen to be the same thing." (D.I. 106 at 793; D.I. 107 at 816–17)

47. The surface described in example 5 was never placed in a biosensor. (D.I. 107 at 934) Dr. Anthony P.F. Turner, Biacore's expert witness, testified that, although one skilled in the art would know that under certain conditions the matrix disclosed in example 5 might contain charged groups that would attract oppositely-charged biomolecules, the resulting concentration, if any, would be insufficient to produce a useful signal. (D.I. 104 at 306–07) According to Dr. Turner, the concentration of ligands necessary to produce a useful signal would vary depending on a number of factors, including the use of the biosensor and the activity of the biological receptor being used. (D.I. 104 at 307)

48. With respect to claims 1 and 15, the '470 patent does teach a hydrogel that is both bound to a surface and activated to contain charged and reactive groups. Relevant to claims 9–11, the charged and reactive groups disclosed are carboxyl groups, some of which are in the form of reactive esters. The '470 patent, however, does not teach the use of charged groups for concentrating oppositely-charged biomolecules. Nor does the '470 patent teach that the ionic concentration should be such that electrostatic concentration can be achieved.[18] (D.I. 104 at 256–57, 305; D.I. 107 at 928–29)

49. With respect to claim 2, the '470 patent teaches the use of a hydrogel that is a swellable organic polymer. (D.I. 107 at 817) With respect to claims 3–4, the '470 patent does not teach the use of a polysaccharide, or more specifically, the use of dextran. (D.I. 107 at 816–17)

50. **The teachings of the Onyezili reference.** The Onyezili reference addresses the immobilization of the enzyme urease inside nylon tubes, a procedure used in medical biochemistry. (DX 533) More particularly, the reference teaches the use of polysaccharide derivatives, specifically a dextran derivative, in order to provide a more hydrophilic coat inside the nylon tubes and to eliminate the nonspecific binding of urease to the tubes. (DX 533 at 121) In the experiment, amino "arms" or "coats" were incorporated into an alkylated nylon tube by filling the tube with the polyamine derivative of dialdehyde dextran ("DPA").[19] (DX 533 at 121–23) The tube was activated by filling it with glutaraldeh-

18. In an *ex parte* experiment, Dr. Scouten "replicated" example 5 of the '470 patent. (D.I. 107 at 818–23; DX 574 at 16–18) His results indicated that the hydrogel disclosed in example 5, in fact, did contain charged groups capable of bringing about, and actually brought about, a concentration of oppositely-charged biomolecules and reactive groups capable of covalently binding the concentrated biomolecules. (D.I. 107 at 818–22; DX 574) However, Dr. Scouten chose the conditions under which to conduct the experiment since they are not set forth in the patent itself. Thus, the results of his experiment are of little probative value since it cannot be ascertained with any certainty whether Dr. Scouten created the same polymer disclosed in example 5. Moreover, Dr. Scouten never placed the surface he created in a biosensor to determine its functionality.

19. The polyamine derivative of dialdehyde dextran was prepared in part by subjecting dialdehyde dextran to periodate oxidation. (DX 533 at 121) According to Biacore, Thermo's own researchers had abandoned this method, finding that there was no significant difference in ligand binding between the oxidized dextran and the bare biosensor surface. (D.I. 114 at 28; PX 65 at 109239) The Thermo researchers theorized that this was due to periodate breakdown of the glycosidic bonds in the dextran. (PX 65 at 109239) In making this argument, however, Biacore relies on a technical document that was not discussed with any witness at trial. Therefore, the court is unable to determine the weight to be afforded Biacore's argument.

yde in a borate buffer. (DX 533 at 121–23) Subsequently, the tube was filled with a solution of urease, an enzyme that converts urea into ammonia. (DX 533 at 121–23) The activity of the immobilized urease was determined by measuring the enzyme-catalyzed hydrolysis of urea in EDTA buffer, i.e., by assaying the effluent for ammonia. (DX 533 at 121–23)

51. With respect to claims 1 and 15, the Onyezili reference teaches a dextran matrix covalently bound to a nylon surface. Said matrix is activated to contain reactive groups (the carbonyl and aldehyde groups of gluteraldehyde). (D.I. 107 at 824–26) According to Dr. Scouten, the matrix also contains charged groups, the amines of the amino DPA "arms" or "coats" that are incorporated into the tube. (D.I. 107 at 927) Dr. Scouten indicated that these groups, although they interact with the gluteraldehyde, retain their positive charge even in the presence of excess gluteraldehyde. (D.I. 107 at 823–24) The reference itself, however, states that

> [m]ore significantly, O-alkylated nylon tubes modified with DPA bound virtually no urease without activation with glutaraldehyde. This observation would suggest that, in these tubes, urease would not be immobilized by nonspecific bonds but would be bound by the covalent linkages between the carbonyl groups (from gluteraldehyde) on the tube and amino groups in the enzyme.

(DX 533 at 124) Dr. Scouten felt that this statement applied "after a washing procedure necessary for use of the material," although there is no indication of such in the reference. (D.I. 107 at 926) Therefore, according to Dr. Scouten, the statement does not suggest that there was no concentration by charge of the urease prior to activation by gluteraldehyde. (D.I. 107 at 926) He conceded, however, that nothing in the reference indicated that concentration by charge occurred. (D.I. 107 at 926)

52. Dr. Scouten also conceded, assuming arguendo the presence of charged groups, that the reference does not disclose explicitly the use of charged groups for bringing about a concentration of oppositely-charged biomolecules. (D.I. 107 at 923) He also admitted that, if what is required first is concentration of biomolecules by charged groups, then the reference also does not teach reactive groups that function to covalently bind biomolecules having been so concentrated. (D.I. 107 at 923–24) He testified, however, that the reference does report reactive groups for covalently binding biomolecules. (D.I. 107 at 924)

53. Dr. Scouten also admitted that the Onyezili reference does not disclose a biosensor as that term is defined in the '161 patent. (D.I. 107 at 922–23) Accordingly, he conceded that the reference does not teach the use of a matrix in a biosensor. (D.I. 107 at 922–23) The reference does not describe the element used to monitor the binding event. (D.I. 107 at 922–23) Specifically, the article does not indicate whether the method for detecting ammonia in the effluent involved manual assay or the use of a transducer. (D.I. 107 at 922–23) According to Dr. Scouten, had the reference described employment of the latter, then it would have disclosed the use of a biosensor as defined in the '161 patent. (D.I. 107 at 922–23) It was Dr. Scouten's opinion, however, that the surface disclosed in the Onyezili reference is suitable for use in a variety of types of biosensors. (D.I. 107 at 823)

54. With respect to claims 2–4, the reference teaches the use of a polysaccharide hydrogel, specifically dextran. With respect to claim 10, the reference discloses a matrix coating wherein the charged groups are amines and the reactive groups are carbonyl and aldehyde groups.

55. **The teachings of the Mandenius reference.** The Mandenius reference reports the findings of an affinity-based study in which the reversible affinity bind-

ing of NAD [20]-dependent deh
an NAD-coated silicon surf
tored using a reflectometer.
part of the experiment, aft
silicon chips were coated w
T500 [21] dextran in order to "
ble nonspecific binding. (D
85; D.I. 107 at 906–08)
groups of the dextran were
tresyl chloride after which
were covalently fixed to th
the time course of affinity
sured.[22] (DX 530 at 283–85)

56. With respect to clai
15, the reference teaches
biosensor (reflectometer) of
trix coating bound to a s
(D.I. 107 at 827–30) The hy
vated to contain reactive
form of tresyl groups, tresy
of sulfonyl ester which acts
molecular gluing agent." (D
30) With regard to the prese
groups, Dr. Scouten opined
possesses an inherent negat
to the presence of carboxyl
polysaccharide. (D.I. 107
discussion *infra* at Part II.
puted that activation of the
tresyl chloride would not re
corporation within the hydro
carboxyl groups.

57. The reference does n
plicitly the use of a matr
charge. (D.I. 107 at 911)
does not teach the use of c
for concentrating oppositely
olecules. (D.I. 107 at 918–1

20. NAD stands for nicotinam
nucleotide. *Dictionary of B*

21. While the "T" refers to "t
the number refers to the mol
the dextran, in this case 500,0

22. Biacore researchers dete
their own experiments that
with tresyl chloride was uns
a biosensor. (D.I. 103 at 1
searchers, conducting their o
reached this same conclusio
however, questioned the tec

ing of NAD[20]-dependent dehydrogenase to an NAD-coated silicon surface was monitored using a reflectometer. (DX 530) As part of the experiment, after silanization, silicon chips were coated with a layer of T500[21] dextran in order to "bypass" possible nonspecific binding. (DX 530 at 283–85; D.I. 107 at 906–08) The hydroxyl groups of the dextran were activated using tresyl chloride after which NAD analogs were covalently fixed to the surface and the time course of affinity binding measured.[22] (DX 530 at 283–85)

56. With respect to claims 1, 11, and 15, the reference teaches the use in a biosensor (reflectometer) of a dextran matrix coating bound to a silicon surface. (D.I. 107 at 827–30) The hydrogel is activated to contain reactive groups in the form of tresyl groups, tresyl being a kind of sulfonyl ester which acts like "a sticky molecular gluing agent." (D.I. 107 at 827–30) With regard to the presence of charged groups, Dr. Scouten opined that dextran possesses an inherent negative charge due to the presence of carboxyl groups in the polysaccharide. (D.I. 107 at 827–30; *see* discussion *infra* at Part II.G) It is undisputed that activation of the dextran with tresyl chloride would not result in the incorporation within the hydrogel of charged carboxyl groups.

57. The reference does not disclose explicitly the use of a matrix carrying a charge. (D.I. 107 at 911) Accordingly, it does not teach the use of charged groups for concentrating oppositely-charged biomolecules. (D.I. 107 at 918–19) In fact, dextran was selected in order to avoid nonspecific binding:

> To bypass possible nonspecific binding we decided first to coat the silicon chip used with dextran as this has previously been shown to allow fibrinogen to be desorbed conveniently from a silicon surface by buffer solutions which otherwise would not have been possible ....

(DX 530 at 283) Nor does the Mandenius reference teach that the alleged inherent charge of the dextran matrix, or the incorporation of charged groups in a dextran matrix, will be beneficial in bringing about a concentration of oppositely-charged biomolecules. (D.I. 107 at 911–12, 918–19) Dr. Scouten averred, however, that one of ordinary skill in the art would know that inherent in dextran are charged carboxyl groups. (D.I. 107 at 911) He further opined that one of ordinary skill would have recognized that charged groups would be advantageous because they would facilitate concentration of the enzyme into the gel. (D.I. 107 at 910) Dr. Scouten pointed to the fact that in the reference the dextran-coated chips were activated by tresyl chloride dissolved in pyridine, a base. (D.I. 107 at 913–14) According to Dr. Scouten, under those conditions, the carboxyl groups inherently present in the dextran would have been negatively charged. (D.I. 107 at 913–14)

58. The structure disclosed in the Mandenius reference that Dr. Scouten contended met the conditions of claim 1 was not used in a biosensor. Instead, that structure was further treated with a relatively high concentration of NAD in a sodium

20. NAD stands for nicotinamide adenine dinucleotide. *Dictionary of Biochemistry* 317.

21. While the "T" refers to "technical grade," the number refers to the molecular weight of the dextran, in this case 500,000 daltons.

22. Biacore researchers determined through their own experiments that dextran modified with tresyl chloride was unsuitable for use in a biosensor. (D.I. 103 at 194) Thermo researchers, conducting their own experiments, reached this same conclusion. Dr. Scouten, however, questioned the technique employed by Dr. Robert Davies, the head of Thermo's biosensor surface development program, in carrying out the tresyl chloride experiments. (D.I. 107 at 903–05) According to Dr. Scouten, Dr. Davies deviated from the teachings of the published article he was following when he conducted the experiments. (D.I. 107 at 903–05) Dr. Davies' conduct caused Dr. Scouten to question whether Dr. Davies was a person of ordinary skill in the art, despite the fact that Thermo considered him its most experienced scientist with regard to ligand immobilization. (D.I. 107 at 903)

phosphate buffer (0.1 M, pH 7.5, no longer basic conditions) in order to effect ligand immobilization before its use in a biosensor. (D.I. 107 at 914, 917–18) According to Dr. Scouten, "those conditions may or may not cause concentration of the NAD," which still would have been positively charged at that pH. (D.I. 107 at 915, 917–18) Dr. Scouten opined, although he had "not looked up the binding of NAD," that

> there are conditions [under which] this material that Mandenius describes would be very useful in making a biosensor and that the actual use of that would both have the charged groups concentrating the biomolecules and the reactive groups binding to the biomolecules that were concentrated.

(D.I. 107 at 918)

59. With respect to claims 2–4, the hydrogel taught in the reference is dextran, a polysaccharide. (D.I. 107 at 830)

60. **The teachings of the Scouten paper.** The Scouten paper teaches methods for immobilizing fluorescent-labeled bovine serum albumin ("BSA") on cellulose membranes. (DX 524) These membranes are incorporated into a fiber optic probe used to monitor bilirubin concentrations directly in the bloodstream. (DX 524) One method taught in the paper involves treating dialysis membranes[23] with polyethylenimine and then reacting those membranes with a gluteraldehyde solution. (DX 524 at 120–21) Fluorescent-labeled BSA then is added to the membranes and allowed to react. (DX 524 at 120–21)

61. With respect to claims 1 and 15, the Scouten paper teaches the use in a fiber optic biosensor of a polyethylenimine hydrogel bound to a dialysis membrane. The hydrogel is activated to contain reactive groups in the form of aldehyde and vinyl groups of glutaraldehyde. (D.I. 107 at 832–34) According to Dr. Scouten, the hydrogel also has incorporated into it positively-charged amine groups—these groups being part of the polyethylenimine's backbone. (D.I. 107 at 832–34, 939–40)

62. Dr. Scouten conceded that this paper does not disclose charged groups that are functioning to bring about a concentration of biomolecules carrying an opposite charge. (D.I. 107 at 939–40) He also admitted that the article does not teach that one should employ conditions that would allow the charged groups to electrostatically attract biomolecules into the matrix. (D.I. 107 at 939–40) In fact, the conditions under which Dr. Scouten employed the structure are not set forth in the reference except to state the use of a phosphate buffer, the pH of which is unspecified. (D.I. 107 at 941–43) Dr. Scouten never performed any tests to determine whether or not electrostatic concentration occurred under the experimental conditions he employed in developing the disclosed procedure. (D.I. 107 at 943)

63. With respect to claims 2–4, polyethylenimine is a swellable organic polymer, but it is not dextran. With respect to claim 10, the disclosed matrix coating is activated to contain charged groups that are amines and reactive groups that are aldehyde and vinyl groups.

64. Dr. Scouten opined generally that it would have been apparent to one of skill in the art possessing knowledge of organic chemistry that incorporated in the matrix coatings disclosed in the aforementioned references are charged groups that would act, under the proper conditions, to attract and concentrate ligands. (D.I. 107 at 835–36) Moreover, Dr. Scouten opined that one of ordinary skill in the art would have known from, for example, ion exchange chromatography literature, of the conditions, i.e., the pH, necessary to take advantage of the charged groups to concentrate the desired biomolecules prior to covalent binding. (D.I. 106 at 781; D.I. 107 at 964)

23. Dialysis membranes are comprised of cellulose that has been dissolved until it becomes amorphous and then reprecipitated into a particular form. (D.I. 107 at 832–34)

65. **The teachings of the vey article.** The 1987 Scou ticle lists a number of metl lently coupling enzymes tc matrices. (DX 518 at 38–4 the article mentions the use ide as a coupling agent wi agarose and cellulose matri at 38–41) In addition, it discl of activation reagents that hydrogels, including hydraz droxysuccinimide ("NHS"), can be employed to prov charged groups on a ("CM")-dextran hydrogel ma at 54–55)

66. **The teachings of reference.** The Akanuma closes in the context of affin raphy a method for the conv Sephadex (cross-linked de hydrazide derivative. (DX ly, the reference discloses whereby CM–Sephadex is carbodiimide, resulting in tl ester linkages, i.e., the form rings on the dextran deriva at 1358–60) The resultant b ed with hydrazine to form h nylmethyl-Sephadex, a hyc tive of CM–Sephadex. (D 1360–61) Analysis of the pro revealed that more than 9 boxyl groups were converte groups. (DX 519 at 1360) "propose[s]" the use of this a general and effective n conversion of carboxy-met ides into their hydrazid (DX 519 at 1360–61)

67. With respect to clair ma reference teaches the u reagents to produce an ac hydrogel matrix having carl

24. In their post trial brief invalidity, Thermo cites to s references that it refers to c "Charged Concentration R Scouten addressed only fiv ences at trial. The court, th its analysis to those five refer

amine groups—these
ɔart of the polyethyleni-
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o bring about a concentra-
ules carrying an opposite
)7 at 939–40) He also ad-
ɜrticle does not teach that
loy conditions that would
ɟ groups to electrostatical-
ɔlecules into the matrix.
40) In fact, the conditions
·. Scouten employed the
, set forth in the reference
the use of a phosphate
of which is unspecified.
1–43) Dr. Scouten never
ɜsts to determine whether
tic concentration occurred
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ping the disclosed proce-
ιt 943)

ɔect to claims 2–4, polye-
ʂwellable organic polymer,
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necessary to take advan-
ed groups to concentrate
ɔlecules prior to covalent
6 at 781; D.I. 107 at 964)

then reprecipitated into a
(D.I. 107 at 832–34)

65. **The teachings of the Scouten survey article.** The 1987 Scouten survey article lists a number of methods for covalently coupling enzymes to a variety of matrices. (DX 518 at 38–41) Specifically, the article mentions the use of carbodiimide as a coupling agent with, *inter alia*, agarose and cellulose matrices. (DX 518 at 38–41) In addition, it discloses a number of activation reagents that are used for hydrogels, including hydrazine and *N*-hydroxysuccinimide ("NHS"), both of which can be employed to provide negatively charged groups on a carboxymethyl ("CM")-dextran hydrogel matrix. (DX 518 at 54–55)

66. **The teachings of the Akanuma reference.** The Akanuma reference discloses in the context of affinity chromatography a method for the conversion of CM–Sephadex (cross-linked dextran) into its hydrazide derivative. (DX 519) Specifically, the reference discloses a procedure whereby CM–Sephadex is treated with a carbodiimide, resulting in the formation of ester linkages, i.e., the formation of lactone rings on the dextran derivative. (DX 519 at 1358–60) The resultant beads are treated with hydrazine to form hydrazinocarbonylmethyl-Sephadex, a hydrazide derivative of CM–Sephadex. (DX 519 at 1358, 1360–61) Analysis of the product so formed revealed that more than 90% of the carboxyl groups were converted to hydrazide groups. (DX 519 at 1360) The reference "propose[s]" the use of this procedure "as a general and effective method for the conversion of carboxy-methylpolysaccharides into their hydrazide derivatives." (DX 519 at 1360–61)

67. With respect to claim 5, the Akanuma reference teaches the use of activation reagents to produce an activated dextran hydrogel matrix having carboxyl groups at least 90% of which are in the form of reactive hydrazides.

68. **The "Charged Concentration References."** [24] The remaining prior art references, the "Charged Concentration References," are indicative of the knowledge as of November 1988 of the concept of charged attraction, i.e., Coulomb's Law.[25] (D.I. 107 at 836) In general, these references teach the combined use of charged and reactive groups in order to enhance ligand immobilization.

69. **The teachings of the Frost reference.** The Frost reference addresses, in the context of affinity chromatography, the effect of protein charge on immobilization. (DX 527) Specifically, the experiments described were conducted to determine the optimal conditions for immobilization of acidic, neutral, and basic proteins to a matrix coating, said matrix coating being either an uncharged (Affi–Gel 10) or a positively charged (Affi–Gel 15) NHS ester derivative of agarose. (DX 527 at 163–64) The results of the study indicate "that an important factor which determines the level of immobilization of a given protein using active ester gels is the net charge on the protein relative to the net charge on the ... [matrix], at the specific pH used for immobilization." (DX 527 at 167)

70. **The teachings of the Shukla reference.** The Shukla reference compares the immobilization of acidic proteins for an NHS ester derivative of cross-linked agarose beads containing a positively charged spacer arm with that for an NHS-activated gel with an uncharged spacer arm. (DX 528) The results of the study show that the amount of protein immobilized to the positively-charged agarose was "appreciably higher" than the amount bound to the gel

24. In their post trial brief on the issue of invalidity, Thermo cites to seven (7) prior art references that it refers to collectively as the "Charged Concentration References." Dr. Scouten addressed only five of these references at trial. The court, therefore, will limit its analysis to those five references.

25. Coulomb's law is an expression for the electrostatic force between two point charges; the force is repulsive if the charges have the same sign and attractive if the charges have the opposite sign. *See Dictionary of Biochemistry* 104.

with the uncharged spacer. (DX 528 at 296) The reference attributes this difference in coupling efficiency "to interaction between the positively charged, protonated tertiary amine of the spacer arm and the net negative charge of the proteins, buffered at a pH above their isoelectric points." (DX 528 at 296)

71. **The teachings of the Torchilin reference.** The Torchilin reference examines the effect of electrostatic complex formation on enzyme immobilization using ionogenic carriers. (DX 531) The results of the study indicate that electrostatic complex formation between an ionogenic carrier and a ligand prior to immobilization increases the amount of immobilized enzyme. (DX 531 at 22) Furthermore, the results demonstrate "that for successful complex formation some minimal number of charged groups in the carrier should exist. Under this limit the complex formation does not take place ..." even under favorable conditions. (DX 531 at 24) The reference concludes by suggesting that "in immobilization of enzymes and other biologically active compounds on ionogenic carriers by covalent binding, electrostatic complex formation between the protein and the carrier can be successfully used. This allows the binding of larger amounts of active enzyme and a significant increase in the stability of the products." (DX 531 at 27)

72. **The teachings of the Crook patent.** The Crook patent discloses a "polymeric matrix having a biologically active substance chemically bound thereto, which comprises a polymer and a biologically active substance ... linked by" a triacin compound. (DX 540, col. 6, lns. 27–42) The patent further discloses a process for producing said polymeric matrix wherein the biologically active substance is one of a particular set of enzymes and the triacin compound has attached thereto a nucleophilic substituent that is an amino acid,

> preferably one that carries a positive charge when in contact with solutions having a pH in the normal biological range, that is to say the range within which biological reactions will proceed .... Groups that are electrically neutral or that carry a negative charge can be used in some circumstances, but it has been found that the presence of such a positive charge frequently assists the reaction of a biologically active substance with the polymer.

(DX 540, col. 7, ln. 7—col. 8, ln. 4; col. 1, lns. 59–68) The patent indicates that polymers suitable for use in forming the matrix include cellulose, cross-linked dextran (e.g., Sephadex by Pharmacia of Uppsala, Sweden), starch, and dextran. (DX 540, col. 6, lns. 64–65; col. 2, lns. 68–73) The specification cites as potential uses of the disclosed polymeric matrices "luciferase system[s] for A.T.P. estimation, biochemical fuel-cells," and "enzymatic analysis, particularly in the sequential analysis of proteins, R.N.A. and D.N.A." (DX 540, col. 3, lns. 51–58) All of these uses, according to Dr. Scouten, are "for or in a biosensor." (D.I. 106 at 779)

73. **The teachings of the Bio-Rad Bulletin.** The Bio-Rad bulletin attributes the difference in coupling efficiency of the Affi-Gel 10 and Affi-Gel 15 supports

> to interaction between the charge on the protein and charge on the gel. Hydrolysis of some of the active esters during aqueous coupling will impart a slight negative charge to Affi-Gel 10. This negative charge will attract positively charged proteins (proteins buffered at a pH below their isoelectric point) and enhance their coupling efficiency. Conversely, the negative charge will repel negatively charged proteins (proteins buffered at a pH above their isoelectric point) and lower their coupling efficiency. Affi-Gel 15, due to the tertiary amine incorporated into its arm, has a slight overall positive charge, and the effects are reversed.

(DX 951 at 2) The bulletin dictates the conditions, e.g., isoelectric point and pH, necessary to take advantage of the

charged groups to attract bi
or to covalent bonding. (D

G. The Scope of the '161

74. Claim 1 of the '16
generic claim directed to a
trix coating suitable for use
Despite the high level of com
field following publication of
cle demonstrating the practi
of evanescent wave technol
sensor, few, if any, function
devices made it through d
market. (PX 35 at 94) Th
developed employed planar
virtually all of them "attach
layer of biological recognit
... directly to the evanescer
surface by physical adsorptic
106; D.I. 104 at 272) These
not overcome the aforemer
problems of capacity, activit
cific binding. Until the laun
first biosensor system in 19
no affinity-based devices o
(D.I. 103 at 72)

75. The matrix coating
claim 1 comprises a hydrog
bound to a surface and capa
the desired ligands. At th
invention, hydrogels in and
and in matrix form were n
but their employment for li
zation had been documented
224, 300–02; D.I. 106 at 761
November 1988, hydrogels
on surfaces in biosensors, al
fashion claimed in the '161
103 at 186, 196–97; D.I. 104
D.I. 106 at 793) Furthermo
of binding a hydrogel to a
metal and nonmetal, were kı
at 793)

76. The hydrogel claime
patent is activated to contai
groups for concentrating bi
reactive groups for covalent
concentrated biomolecules.
vember 1988, it was known t
charged groups and reactiv

charged groups to attract biomolecules prior to covalent bonding. (D.I. 107 at 964)

G. The Scope of the '161 Patent

74. Claim 1 of the '161 patent is a generic claim directed to a hydrogel matrix coating suitable for use in a biosensor. Despite the high level of competition in the field following publication of the 1983 article demonstrating the practical application of evanescent wave technology in a biosensor, few, if any, functional commercial devices made it through development to market. (PX 35 at 94) Those that were developed employed planar surfaces and virtually all of them "attached the sensing layer of biological recognition molecules ... directly to the evanescent wave sensor surface by physical adsorption." (PX 35 at 106; D.I. 104 at 272) These biosensors did not overcome the aforementioned salient problems of capacity, activity, and nonspecific binding. Until the launch of Biacore's first biosensor system in 1990, there were no affinity-based devices on the market. (D.I. 103 at 72)

75. The matrix coating disclosed in claim 1 comprises a hydrogel that is both bound to a surface and capable of binding the desired ligands. At the time of the invention, hydrogels in and of themselves and in matrix form were not only known but their employment for ligand immobilization had been documented. (D.I. 104 at 224, 300–02; D.I. 106 at 761) Moreover, by November 1988, hydrogels had been used on surfaces in biosensors, albeit not in the fashion claimed in the '161 patent. (D.I. 103 at 186, 196–97; D.I. 104 at 224, 300–01; D.I. 106 at 793) Furthermore, the means of binding a hydrogel to a surface, both metal and nonmetal, were known. (D.I. 106 at 793)

76. The hydrogel claimed in the '161 patent is activated to contain both charged groups for concentrating biomolecules and reactive groups for covalently binding the concentrated biomolecules. Prior to November 1988, it was known to provide both charged groups and reactive groups on a polysaccharide gel for immobilizing ligands. (D.I. 104 at 240, 323–24; D.I. 106 at 767–68) Likewise, the literature had described hydrogels bound to a surface for use in a biosensor, which hydrogels contained both reactive groups and groups that could be charged. (D.I. 104 at 304, 323–24; D.I. 107 at 835–37) Prior to November 1988, the literature also taught in the context of biosensor technology the use of dextran modified with reactive groups to covalently bind biomolecules. (D.I. 104 at 300–01) Moreover, the activation chemistries necessary to effectively incorporate charged and reactive groups into a hydrogel, particularly a dextran hydrogel, were not only known in the art but had been employed in the context of ligand immobilization. (D.I. 104 at 234, 245–46; D.I. 106 at 763, 765, 767) It was also known that the result of such activation would be the presence of charged groups with the ability to immobilize ligands. (D.I. 104 at 234, 245–46; D.I. 106 at 763, 765, 767)

77. Dr. Scouten opined that as of November 10, 1988 it would have been obvious to one of ordinary skill in the art who wanted to do the type of ligand immobilization disclosed in the '161 patent to have used both charged and reactive groups. (D.I. 107 at 900) Dr. Turner opined, however, that the literature, although it taught the presence in a hydrogel of groups that could be charged, did not teach that those groups, if charged, could, under the proper conditions, bring about the concentration of biomolecules. (D.I. 104 at 304) It was Dr. Turner's opinion that the literature, particularly that in the area of affinity chromatography, taught the use of a neutral hydrogel, such as dextran, so as to reduce the incidence of nonspecific binding. (D.I. 104 at 304)

78. As of November 1988, the literature with respect to affinity chromatography taught generally that charge in the matrix was to be avoided. "[A]ffinity chromatography is realized by covalently attaching a specific ligand which interacts with the desired macromolecule to an inso-

luble inert support." (PX 20 at 12) It involves the "immobilization of an appropriate ligand in such a way that the enzyme is still capable of recognizing and binding to the immobilized form of the ligand, whereas contaminating proteins . . . have no such recognition." (PX 490 at 531) Although the presence of charged entities in most enzyme immobilizations is not an important problem, in affinity chromatography "a combination of ion exchange and affinity can be either fortunate or unfortunate, depending upon charge and types of impurities, etc., to be removed by the chromatographic process." (PX 489 at 290) Accordingly, in the context of affinity chromatography an inert matrix or support was desired in order to avoid the nonspecific adsorption of proteins.

79. An article on affinity chromatography authored by Dr. Scouten stresses the importance of "the selection of the appropriate inert [i.e., nonreactive] matrix," stating that "[n]onspecific adsorption must not occur in the derivatized matrix." (PX 490 at 532) Among the many potential matrices for affinity chromatography cited by Dr. Scouten are dextran-coated glass, which he indicates exhibits "little or no adsorption," and cross-linked dextrins, which are related to cross-linked dextrans. (PX 490 at 532–33, 540) He notes that most of the matrices used for immobilization of enzymes have possible application in bioselective adsorption[26] but that few "have been used because of their potential for nonspecific adsorption either by charge . . . or by hydrophobic interactions." (PX 490 at 540) In the article, Dr. Scouten also emphasizes that attachment of ligands to the matrix must be performed in a manner that no charged, ionogenic, or hydrophobic residues remain after derivatization, which, he notes, is a "fact which has only recently been appreciated, and therefore must be kept in mind when reviewing the earlier literature." (PX 490 at 541; D.I. 107 at 885–86)

80. Dr. Scouten agreed that the literature indicated a researcher would want to avoid charged groups in affinity chromatography in order to reduce nonspecific binding. (D.I. 107 at 908) He asserted, however, that affinity chromatography is not the equivalent of enzyme immobilization generally much less enzyme immobilization in the context of biosensor technology. (D.I. 107 at 910) Dr. Scouten viewed affinity chromatography as a use of an immobilized ligand, not the immobilization of a ligand. (D.I. 107 at 945–49, 958–60) According to Dr. Scouten, the conditions for the two need not be the same, i.e., depending on the circumstances, particularly with respect to the desired use and/or function, the presence of charged groups in a matrix might be advantageous, might be problematic, or might be immaterial. (D.I. 107 at 945–49, 958–60) Thus, it was Dr. Scouten's belief that nonspecific binding is not a problem with respect to all biosensors. (D.I. 107 at 908–09) Dr. Scouten concluded that one skilled in the art who was familiar with the literature would be able to predict the conditions and charge concentrations desired for his/her desired use and/or function. (D.I. 107 at 945–49, 958–60)

81. Dr. Scouten also disagreed with Dr. Turner's assessment of dextran as being noncharged under normal circumstances. (D.I. 104 at 233; D.I. 107 at 889) Dextran is a naturally occurring polysaccharide that has both hydroxyl and carboxylic acid groups. (D.I. 107 at 890) These latter groups, according to Dr. Scouten, are either oxidized moieties or carboxyl groups that are naturally present from carboxyl-containing sugars. (D.I. 107 at 890) According to Dr. Scouten, the carboxylic acid groups incorporated within dextran confer upon the polysaccharide enough inherent charge to bring about a concentration of

26. In bioselective adsorption, a type of affinity chromatography, affinity is based on biologically relevant binding. (PX 490 at 531)

oppositely-charged biomol
106 at 782, 786–87; D.I. 1(
DX 517, DX 577, DX 573)

82. Dr. Scouten never te
dextran used in the examp
patent, to see if it did in
charge. Nonetheless, he
that it did given its nature.
892) Dr. Scouten, however,
dex, a dextran that has be
into bead form with epic
give a three-dimensional ne
meric chains. (D.I. 107 at
periments performed by D
purposes of this litigation
Sephadex does possess cha
acid groups, which groups l
not believe to be the resu
linking itself. (D.I. 106 at
889–91; DX 576) The liter
Dr. Scouten's determinat
the charged state of Sephad

> Although Sephadex can
> being essentially neutr
> small amount of res
> charge in the purified, c
> saccharide presumably
> boxylic acid groups. Th
> nated by condensation o
> groups with glycinamide
> soluble carbodiimide.

(DX 517 at 7; *see also*
(finding that the data de
the results of gel filtrati
were effected by a variet
cluding "the small amount
boxylic groups in the" Seph

83. Dr. Scouten's belie
charged state of dextran
those of the Thermo resea

27. Technical grade dextran
least purified and, therefore
treatment that would remov
ring carboxyl residues. (
Consequently, if Dr. Scou
garding the charged state o
ring dextran are accurate, T
est potential for electrosta
107 at 892)

28. The T500 dextran was a
reactive groups (succinim

Cite as 79 F.Supp.2d 422 (D.Del. 1999)

oppositely-charged biomolecules. (D.I. 106 at 782, 786–87; D.I. 107 at 889; *see* DX 517, DX 577, DX 573)

82. Dr. Scouten never tested T500, the dextran used in the examples in the '161 patent, to see if it did in fact possess a charge. Nonetheless, he was convinced that it did given its nature.[27] (D.I. 107 at 892) Dr. Scouten, however, did test Sephadex, a dextran that has been cross-linked into bead form with epichlorohydrin to give a three-dimensional network of polymeric chains. (D.I. 107 at 890, 965) Experiments performed by Dr. Scouten for purposes of this litigation revealed that Sephadex does possess charged carboxylic acid groups, which groups Dr. Scouten did not believe to be the result of the cross-linking itself. (D.I. 106 at 785; D.I. 107 at 889–91; DX 576) The literature supports Dr. Scouten's determinations regarding the charged state of Sephadex:

> Although Sephadex can be regarded as being essentially neutral, there is a small amount of residual negative charge in the purified, crosslinked polysaccharide presumably caused by carboxylic acid groups. This can be eliminated by condensation of these carboxyl groups with glycinamide using a water-soluble carbodiimide.

(DX 517 at 7; *see also* DX 577 at 341 (finding that the data demonstrated that the results of gel filtration experiments were effected by a variety of factors, including "the small amount of ionized carboxylic groups in the" Sephadex))

83. Dr. Scouten's belief regarding the charged state of dextran conflicts with those of the Thermo researchers. According to an internal Thermo memorandum prepared by Dr. Davies, experiments conducted to determine the need for anchoring dextran to the RM using epoxy silane revealed that a chip coated with noncarboxylated T500 dextran[28] attracted a greatly reduced amount of protein when compared to a chip without a hydrogel coating. (PX 83 at 109342) Dr. Scouten disagreed with Dr. Davies' evaluation of the data, commenting that it could be that the surface of the chip itself was highly adsorptive to protein and that the dextran coating prevented the protein from reaching the surface. (D.I. 107 at 894–97) In fact, Dr. Scouten felt that the slight shift from baseline exhibited by the unmodified dextran demonstrated that the unmodified dextran, in fact, did concentrate protein, although he could not state how much protein was bound. (D.I. 107 at 897–98)

H. The Biacore Biosensor

84. The Biacore biosensor is composed of three parts: the sensor chip; the microfluidic system, which makes sure that liquids arrive at the sensor chip surface at the correct time and in the correct amounts; and the optical detection system, which measures and monitors the reaction occurring on the sensor surface. (D.I. 103 at 73–74) Biacore holds separate patents on each part of the system. (D.I. 103 at 90)

85. Biacore began marketing its automated, optical biosensor system in the United States in 1990 at a cost of $200,000 per system. (D.I. 96 at 5; D.I. 104 at 361–62) Biacore's biosensor was the first real-time, label-free kinetic[29] analyzer on the

27. Technical grade dextran, as is T500, is the least purified and, therefore, has not had any treatment that would remove naturally occurring carboxyl residues. (D.I. 107 at 892) Consequently, if Dr. Scouten's opinions regarding the charged state of naturally occurring dextran are accurate, T500 has the greatest potential for electrostatic binding. (D.I. 107 at 892)

28. The T500 dextran was activated to contain reactive groups (succinimide esters) using EDC/NHS, a standard activation technique for activating a carboxyl group. (PX 83 at 109342; PX 494 at 78–79, 84) The dextran was not modified, however, to contain charged groups (i.e., it was not carboxylated). (PX 83 at 109342; PX 494 at 78–79, 84)

29. Kinetics is "[t]he rate behavior of a physical or a chemical system." *Dictionary of Biochemistry* 263.

market. (D.I. 103 at 74–77, 101) In fact, at the time of its launch, no other affinity-based biosensors were commercially available. Consequently, in order to succeed Biacore had to create a market for a technology for which there was no existing demand. (D.I. 103 at 76–77) Biacore, therefore, undertook an active and aggressive marketing campaign, targeting life science researchers in both academia and industry.[30] (D.I. 103 at 77, 85)

86. The initial response to Biacore's biosensor was overwhelmingly favorable. (D.I. 103 at 77) Biacore attributed the success of its sensor to the dextran hydrogel matrix since sales of its sensors possessing other types of sensing surfaces were (and continued to be up to the time of trial) markedly lower.[31] (D.I. 103 at 108–09) Although at first researchers did not recognize the significance of Biacore's dextran matrix, they quickly realized it was a landmark achievement in the area of bioanalytical sciences. (D.I. 104 at 276; PX 35) Peter Garland, a Thermo consultant and a commentator in the biosensor field, noted in 1996 that

> [w]hereas physical adsorption could be said to have the finesse of a hurricane dumping boats on a foreshore, the methods more recently developed by Johnsson and colleagues ... are comparable to skil[l]ful anchoring. Although developed for the specific case of covalently coupling molecules to the gold surface of an SPR device, they are applicable with minor modifications to all evanescent wave devices. They have been adapted for RM usage, and could readily be used with advantage in TIRF and ATR techniques.

(PX 35 at BIA 011061) Claire Morgan, a Thermo customer, noted in a 1996 article that

> the two widely available immunosensors are both direct optical systems—the BIAcore and the IAsys—and both have surfaces of carboxylated dextran. These have proved to have very low nonspecific binding in biological matrices and achieve good detection limits for a variety of molecules, but their major impact has been to revolutionize the kinetic rate analysis of biomolecular interactions.

(PX 38 at BIA 010149) Thermo in its own marketing describes the dextran hydrogel matrix as the "original sensor surface for biomolecular interactive analysis and hence the most extensively studied and versatile." (D.I. 96 at 3)

I. Thermo's Search For Biosensor Technology

87. In 1987, Fisons joined a research collaboration with GEC–Marconi and the Institute of Biotechnology, University of Cambridge, charged with the development of an evanescent wave biosensor employing RM technology. (D.I. 105 at 414–15; JX 4 at 101867) RM technology was selected for study because (1) it showed itself to be a very sensitive biosensor; (2) it was easy to manufacture; and (3) it had the potential to be more sensitive than many of the then available biosensors. (D.I. 105 at 416–17) In May 1990 the collaborating researchers gave a presentation to a consultant of Fisons who was to evaluate the progress of the group to date to ascertain whether the work warranted formation of a new company. (D.I. 105 at 424–25) At that presentation Dr. Davies, who at the time was working for the Institute of Biochemistry on the surface chemistry aspect of the biosensor project,[32] proposed using a hydrogel on an RM sensing surface in order to immobilize ligands. (D.I. 105 at

30. Academic labs constitute 60–70% of Biacore's market while industrial labs, pharmaceutical companies, and large research labs constitute 30–40%. (D.I. 103 at 85)

31. The same is true with respect to Thermo's sales: sales of dextran cuvettes dwarf sales for other types. (PX 473; PX 244 at 104175; PX 126 at 108483)

32. Dr. Davies joined Affinity Sensors at the time of its formation in August 1990. At the time of trial, however, he was no longer an employee of Affinity Sensors.

424–25; DX 558 at 100798;
Determining that the rese
formation of a new compar
1990, Fisons created a new
ed exclusively to developi
based upon RM technology.
415–16) This division, Fisons
sor Technology, subseque
known as Affinity Sensors.

88. In September 1990,[33]
Fison's British patent coun
run a patent search of Pharn
on biosensors at the reques
personnel with Affinity Sens
the research staff and man
of Affinity Sensors with a
published PCT application.
426–29, 464–67, 489) The r
well as the managing direc
Sensors, reviewed the PCT a
determined that it did not p
lem to Fison's development
sensor. (D.I. 105 at 426–29
It was their belief that (1) t
were entirely restricted to r
which RM technology does
and (2) the description in th
stricted to X–R–Y chemistry
applicable to the dielectric
Applied Sensors was using
sensors. (D.I. 105 at 426–2
A few weeks later, Colin H.
who was at that time an Af
researcher, discussed the P
with Jones. (D.I. 105 at 430

89. Despite having prop
in May 1990, Dr. Davies
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Search For Biosensor
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424–25; DX 558 at 100798; JX 22 at 109) Determining that the research merited formation of a new company, in August 1990, Fisons created a new division devoted exclusively to developing biosensors based upon RM technology. (D.I. 105 at 415–16) This division, Fisons Applied Sensor Technology, subsequently became known as Affinity Sensors. (D.I. 96 at 3)

88. In September 1990,[33] Steve Jones, Fison's British patent counsel, who had run a patent search of Pharmacia's patents on biosensors at the request of technical personnel with Affinity Sensors, furnished the research staff and managing director of Affinity Sensors with a copy of the published PCT application. (D.I. 105 at 426–29, 464–67, 489) The researchers, as well as the managing director of Affinity Sensors, reviewed the PCT application and determined that it did not present a problem to Fison's development of an RM biosensor. (D.I. 105 at 426–29, 464–67, 489) It was their belief that (1) the PCT claims were entirely restricted to metal surfaces, which RM technology does not involve, and (2) the description in the PCT was restricted to X–R–Y chemistry, which is not applicable to the dielectric surfaces that Applied Sensors was using in its RM biosensors. (D.I. 105 at 426–29, 464–67, 489) A few weeks later, Colin H. Maule, Ph.D, who was at that time an Affinity Sensors' researcher, discussed the PCT application with Jones. (D.I. 105 at 430)

89. Despite having proposed the idea in May 1990, Dr. Davies did not begin experimenting with attaching hydrogels to the sensing surface of an RM biosensor in order to immobilize ligands until in or about June 1991. (D.I. 105 at 430–31; JX 22 at 109) Prior to this time, the researchers at Affinity Sensors had experimented with a number of surface materials and chemistries, including adsorption, phenethylsilane, aminosilane-gluteraldehyde, and lanthanum chloride. (D.I. 105 at 431–34; PX 446) Although not failures per se, none of these attempts yielded a surface capable of immobilizing the requisite concentration of ligands. (D.I. 105 at 460–65, 483–85) Dr. Davies indicated in his laboratory notebook that as of May 20, 1991, he had

> had no success in increasing the amount of human IgG adsorbed to the resonant mirror by the surface treatments so far employed.... Maximizing the attractive electrostatic forces probably only increases the initial rate of adsorption, but in these exper[iments] we found no benefit in increasing the electrostatics. Glutaraldehyde activated aminosilanized surfaces seemed to be the best from the view of resistance to detergent elution. However it is probably likely, in my view, that covalent immobili[z]ation to a solid surface will reduce the binding activity of the antibody.

(JX 22 at 107322)

90. Dextran was the first hydrogel selected by Dr. Davies for experimentation. It was selected because prior research involving dextran had shown it to work in similar systems. (D.I. 105 at 455–56; PX 61 at 109250; PX 494 at 72–73) Specifically, Dr. Davies used T500 dextran purchased from Pharmacia. (D.I. 105 at 457) Although the Affinity Sensors researchers experimented with dextrans other than T500 (e.g., dextrans from suppliers other than Pharmacia and dextrans of varying molecular weight), T500 dextran remained their hydrogel matrix of choice for the better part of the 1991–1995 time period. (D.I. 105 at 477–80) Other hydrogels were not substituted for the CM-dextran primarily because it worked well and it was not covered by a patent of which the Affinity Sensors researchers were aware. (D.I. 105 at 480)

91. Unlike SPR biosensors, which primarily employ metallic surfaces, RM biosensors employ materials, such as glass, that are transparent to the wavelengths of

33. Also in September 1990, Dr. Davies attended a meeting in Cleveland, Ohio where presentations by Pharmacia representatives revealed that Pharmacia was using a dextran hydrogel in its biosensor. (D.I. 494 at 44–45)

light being used. (D.I. 105 at 417–18) Consequently, the linking chemistry described in the PCT application was not entirely suitable for the Affinity Sensors researchers' purposes. Thus, the researchers were responsible for developing a means of affixing the hydrogel to the nonmetallic surfaces employed in RM biosensors. Moreover, Dr. Davies questioned the benefits of incorporating charged carboxyl groups into a dextran hydrogel:

> Rather than use the method adopted by Pharmacia for their BiaCore devices I have decided to explore a different chemistry. The Pharmacia coupling process may have unwanted effects on our devices, and also residual carboxylate groups may cause nonspecific binding.

(JX 5 at 109229) By late November 1991, however, experiments conducted by the Affinity Sensors scientists had demonstrated the beneficial role of electrostatic attraction in ligand immobilization. (PX 92; PX 93)

92. In early 1996,[34] after several years of experimentation, during which a large number of surface chemistries and surface materials were tested, the scientists at Affinity Sensors finally developed the surface chemistry employed in the IAsys ™ device at the time of trial. (D.I. 105 at 438, 442–44) Essentially the method involves binding the hydrogel disclosed by Pharmacia to the ion surface of a RM biosensor using known linking chemistries. (D.I. 104 at 317–18; D.I. 105 at 460)

93. The off-chip carboxymethylation procedure developed by Affinity Sensors to affix the dextran hydrogel to the nonmetal RM surface involves a two-step progression. In the first step, unbound CM-dextran is made by reacting dextran in solution with bromoacetic acid and sodium hydroxide. (D.I. 105 at 440, 457; DX 565 at 101044; PX 61; PX 494 at 78–79) This unbound CM-dextran then is activated using EDC/NHS to contain a reactive ester in the form of a succinimide ester and charged carboxyl groups. (D.I. 105 at 440, 457; DX 565 at 101044; PX 61; PX 494 at 78–79) In the second step, the unbound and activated dextran is attached to the RM surface using amino groups. (D.I. 105 at 440–41, 442–44, 480–81; DX 565 at 101046–47; PX 494 at 80) The process results in a dextran hydrogel matrix bound to a surface, said hydrogel being activated to contain charged groups and reactive groups that are carboxyl groups, some of which are in the form of succinimide esters. (PX 46 at 3; PX 156; PX 432 at 2–3; PX 494 at 84–86) This sequence of steps was adopted because (1) it allows for greater control over the level of carboxylation and (2) the harsh reactants needed to carboxylate the methyl groups are detrimental to the cuvette surface employed in the IAsys ™ biosensor.[35] (D.I. 105 at 440; PX 494 at 80) Although the progression of steps is reversed, the methodology is equivalent to that described by the Pharmacia researchers in the PCT application. (D.I. 105 at 457–58; PX 494 at 53–54) The CM-dextran that results is the same regardless of the sequence of steps employed. (D.I. 105 at 481, 482–83; PX 104)

94. Affinity Sensors did not attempt to hide the fact that it was employing the sensing surface developed by Biacore in its RM biosensor. Dr. Denise Vera Pollard-Knight, who at the time was a bioscience manager at Fisons, freely admitted at the World Congress on Biosensors held in Geneva, Switzerland in May 1992, that Affinity Sensors' instrument would include a

34. The methods employed by Thermo at the time of trial were developed "some time after [it] had gone commercial." (D.I. 105 at 438) The general sequence of steps employed has been the same, however, since Thermo began marketing the IAsys ™ system. (D.I. 105 at 443)

35. In Thermo's biosensor systems, the activated dextran matrix is bound to the surface of a disposable cuvette. (D.I. 96 at 4) In contrast, the activated dextran matrix is bound to the surface of a disposable "chip" in Biacore's devices. (PX 360 at BIA 003083, BIA 003092)

CM-dextran hydrogel as se
PCT application bound to a
face of an RM biosensor. (D
83) A number of Biacore r
attended this meeting. (D.I
83, 319–20; D.I. 105 at 444–4
a PCT application filed by F
2, 1992 and published on
1992 described the type of bi
development as comprising

> a layer of dielectric mater
> part of which is coupled to
> ble porous matrix contai
> li[z]ed biochemicals....
> niently, the porous matrix
> e.g. a hydrogel selected fr
> consisting of polysacchari
> rose, dextran, carrageenan
> starch, cellulose, and deriv
> e.g. carboxymethyl deriva
> gum, pectin, and a water
> ganic polymer such as pol
> polyacrylic acid, polyacr
> polyethylene glycol.

(JX 2 at 100542) Furthermore
published in *Biosensors and*
in 1993,[36] the authors, resea
at Fisons, stated that the use
dextran layer was the optim
indirect covalent attachment
at dielectric surfaces. (PX 2
authors acknowledged that
"ha[d] been described previo
surfaces for use with senso
SPR" by researchers at Pha
27 at 359; D.I. 104 at 283–85)

95. On March 9, 1993, Aff
gave its first public demonst
IAsys ™ biosensor at the Bio
ciety Meeting in Leeds, Er
568) Biacore representatives
at this demonstration and det
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36. The article, entitled *The Re*
A Novel Optical Sensor for Di
Biomolecular Interactions Par
tions, was authored by P.E. B

CM-dextran hydrogel as set forth in the PCT application bound to a nonmetal surface of an RM biosensor. (D.I. 104 at 282–83) A number of Biacore representatives attended this meeting. (D.I. 104 at 281–83, 319–20; D.I. 105 at 444–47) In addition, a PCT application filed by Fisons on June 2, 1992 and published on December 10, 1992 described the type of biosensor under development as comprising

> a layer of dielectric material, at least a part of which is coupled to a biocompatible porous matrix containing immobili[z]ed biochemicals.... Most conveniently, the porous matrix is a hydrogel, e.g. a hydrogel selected from the group consisting of polysaccharides, e.g. agarose, dextran, carrageenan, alginic acid, starch, cellulose, and derivatives thereof, e.g. carboxymethyl derivatives, xanthin gum, pectin, and a water-swellable organic polymer such as polyvinyl alcohol, polyacrylic acid, polyacrylamide, and polyethylene glycol.

(JX 2 at 100542) Furthermore, in an article published in *Biosensors and Bioelectronics* in 1993,[36] the authors, research scientists at Fisons, stated that the use of a modified dextran layer was the optimal method for indirect covalent attachment of molecules at dielectric surfaces. (PX 27 at 359) The authors acknowledged that this method "ha[d] been described previously for gold surfaces for use with sensors based on SPR" by researchers at Pharmacia. (PX 27 at 359; D.I. 104 at 283–85)

95. On March 9, 1993, Affinity Sensors gave its first public demonstration of the IAsys ™ biosensor at the Biochemistry Society Meeting in Leeds, England. (DX 568) Biacore representatives were present at this demonstration and details of Affinity Sensors' devices were passed on in memorandum form to Biacore management. (DX 568) Two months later, on May 10, 1993, Biacore submitted the '265 continuation application to the PTO. (PX 3)

96. Thermo's first sale of its manual IAsys ™ biosensor in the United States was made in February 1994. (D.I. 96 at 3; D.I. 105 at 448)

J. Thermo's Evaluation of the '161 Patent

97. The '161 patent issued on July 25, 1995. On September 5, 1995, David Fortune, the managing director of Pharmacia, wrote Thermo advising it of the '161 patent's existence. (D.I. 105 at 467; PX 210; D.I. 96 at 4) Dr. Maule discussed the letter's content and the patent's implication with Mr. Fortune at a meeting held on September 7, 1995, the day Thermo received the letter. (D.I. 105 at 468–69; D.I. 96 at 4) Also in attendance were Doug Stewart, Peter Lowe, Jim Molloy, and possibly Dr. Davies. (D.I. 105 at 468–69; D.I. 96 at 4) At the meeting, the attendees discussed (1) whether the '161 patent was valid, (2) whether the IAsys ™ biosensor was covered by the claims of the '161 patent, and (3) whether one of ordinary skill in the art would think that the '161 patent related only to SPR technology and/or only to metal surfaces. (D.I. 105 at 469–74; PX 193) It was decided that Mr. Jones should obtain a copy of the file history of the '161 patent. (D.I. 105 at 469–74; D.I. 96 at 4) On September 8, 1995, Affinity Sensors wrote Pharmacia, stating that it would respond to Pharmacia's letter in due course. (D.I. 96 at 4)

98. The attendees met again on October 5, 1995. (D.I. 105 at 466, 469–74; D.I. 96 at 4; PX 497 at 17–18, 55) This time they were joined by Mr. Jones and David Yorke, another member of Fison's British patent counsel. (D.I. 105 at 466, 469–74; D.I. 96 at 4; PX 497 at 17–18, 55) Once again the discussion concerned whether Affinity Sensors was infringing the '161

36. The article, entitled *The Resonant Mirror: A Novel Optical Sensor for Direct Sensing of Biomolecular Interactions Part II; Applications*, was authored by P.E. Buckle, R.J. Davies, T. Kinning, D. Yeung, P.R. Edwards, and D. Pollard-Knight and published in *Biosensors & Bioelectronics*, Vol. 8, in 1993.

patent. (D.I. 105 at 466, 469–74; D.I. 96 at 4; PX 497 at 17–18, 55) The attendees determined to seek the opinion of an American attorney regarding the validity and scope of the '161 patent. (D.I. 105 at 466, 469–74; D.I. 96 at 4) Mr. Lowe's handwritten notes from this meeting contain the notation "We Infringe!" (PX 193 at 106699)

99. Subsequently, Affinity Sensors' management team contacted Mr. Rodger Van Kirk, Esquire, a U.S. patent attorney, and the firm of Nixon Hargraves. Although counsel was contacted in December 1995 regarding their respective evaluations of the '161 patent,[37] a written opinion was never issued by either Mr. Van Kirk or by the firm of Nixon Hargraves.[38] (D.I. 105 at 474–76) Although thoughts of redesigning the CM-dextran cuvette used in the IAsys ™ biosensor were discussed briefly, no action in this direction was taken. (D.I. 105 at 476; D.I. 96 at 5)

100. On July 24, 1996, Thermo's attorneys filed an amendment to its pending patent application, Serial No. 667,323, directed to its RM biosensor technology.[39] (PX 16, Tab 15) The amendment contains a set of claims that are duplicative of the claims in the '161 patent. (PX 16, Tab 15 at 102137–40) The amendment explicitly states that these claims were copied from the '161 patent.[40] (PX 16, Tab 15 at 102137–40)

101. In a memorandum to Mr. Jones dated November 27, 1996, Dr. Davies commented that "[f]or me the Pharmacia patent was inventive in that it demonstrated electrostatic concentration of protein into a matrix on a surface, and this matrix preserved the activity of the protein coupled to it." (PX 214)

K. The Battle for the Biosensor Market

102. Thermo began selling its manual IAsys ™ biosensor in the United States in February 1994[41] at a price of $80,000. (D.I. 96 at 3; PX 295 at 106039; PX 495 at 145) Since it possessed the activated dextran matrix found in the BIAcore ™ biosensor, the IAsys ™ biosensor was marketed as a low cost alternative to the automated BIAcore ™ system. (PX 22 at 103702; PX 29 at 100091; PX 259 at 103737) In anticipation of Thermo's marketing of the less expensive IAsys ™ device, Biacore introduced in the fall of 1993 a manual biosensor, marketed under the name BIAlite ™. (D.I. 103 at 111; PX 501 at 83–85)

102. Biacore subsequently introduced other versions of its biosensor. In the fall of 1994, Biacore began marketing the automated BIAcore ™ 2000 and, in the spring of 1995, the automated BIAcore ™ 1000. This latter model was a less expensive instrument and possessed fewer features. In the spring of 1996, Biacore introduced the manual BIAcoreX ™. At the same time, it eliminated the original BIAcore ™ biosensor and the BIAlite ™ instruments from its product line. The BIAcore ™ 2000 is Biacore's largest selling instrument.

104. At the time of trial, Thermo marketed three different biosensors in the

37. The content of these discussions was not disclosed to the court.

38. On September 18, 1996, Thermo filed a prospectus with the U.S. Securities and Exchange Commission wherein it stated that it had not obtained an opinion of counsel with respect to the '161 patent. (D.I. 96 at 5)

39. This application claimed an effective filing date of June 4, 1991, based on a United Kingdom patent application. (PX 16, Tab 1 at 100519)

40. At trial, Thermo asserted that it had copied the claims in order to provoke an interference action challenging the validity of the '161 patent claims before the PTO pursuant to 35 U.S.C. § 135.

41. Although the first sale did not occur until early 1994, demonstration models were available in 1993.

United States: (1) the manual IAsys™ instrument; (2) the automated IAsys™ auto+; and (3) the automated IAsys™ auto+ advantage. (D.I. 96 at 3) Thermo's first sale of an automated system in the United States occurred on May 21, 1996. (D.I. 96 at 3) The manual IAsys™ device continued to be Thermo's largest selling biosensor at the time of trial.

105. Along with the device itself, Thermo provides its customers with instructional materials regarding the use of the IAsys™ biosensor. Among other things, the customers are given a Methods Guide (PX 169) and Protocol 1.1 (JX 20) that inform them how to convert some but not all of the carboxyl groups on the CM-dextran to reactive succinimide esters. The manuals go on to instruct the customers how to use the CM-dextran cuvette in the biosensor in order to electrostatically concentrate ligands into the dextran matrix and covalently bind ligands so concentrated. (JX 20; PX 169) In addition, Thermo supplies its customers with application notes and promotional literature demonstrating the benefits and uses of the IAsys™ biosensor. (JX 8–19; PX 141–143: PX 147)

106. In addition to its CM-dextran cuvette, at the time of trial, Thermo offered for sale cuvettes bearing aminosilane, biotin, carboxylate, hydrophobic, and uncoated surfaces. (D.I. 105 at 502–06) All of these cuvettes are interchangeable to the extent that they all fit into the IAsys™ biosensor. (D.I. 105 at 506) Each surface possesses unique properties making it suitable for particular applications. (D.I. 105 at 502–06, 512–16) There is, however, enough overlap between the properties, features, and particular uses of each surface that the nondextran cuvettes "cover all the things that dextran [cuvettes] can do." (D.I. 105 at 532, 539–41) Until 1996, Thermo offered for sale only CM-dextran and aminosilane cuvettes. (D.I. 106 at 664) The biotin and carboxylate surfaces were introduced in 1996 and the hydrophobic surface in 1997. (D.I. 106 at 520, 523)

III. CONCLUSIONS OF LAW

A. Jurisdiction

1. As a threshold matter, Biacore argues that the court lacks subject matter jurisdiction with respect to all claims of the '161 patent other than claims 4 and 5. Biacore originally accused Thermo of infringing the '161 patent generally by the manufacture, use, and sale of biosensor systems embodying the claimed invention. (D.I.1) Thermo counterclaimed seeking declaratory judgment, pursuant to the Declaratory Judgment Act, 28 U.S.C. § 2201, of noninfringement and invalidity of the '161 patent. (D.I.6) Although identifying in the pre-trial order claims 1–5, 9–11, and 15 of the '161 patent as being infringed by Thermo, Biacore on the first day of trial limited "for the purposes of the trial" its charges to claims 4 and 5. (D.I. 96; D.I. 103 at 4) Biacore, therefore, asserts that the court has no jurisdiction over claims 1–3, 9–11, and 15 because a "a case or controversy" no longer exists with respect to those claims. (D.I. 114 at 21 n. 21) Thermo disagrees, stating that its counterclaim of invalidity still exists even after Biacore's withdrawal. (D.I. 112 at 2 n. 1)

[1] 2. It is axiomatic that a case or controversy is a jurisdictional predicate for declaratory judgment under § 2201. *See Grain Processing Corp. v. American Maize–Prods.*, 840 F.2d 902, 905 (Fed.Cir. 1988). This requirement precludes a party from asserting a claim of noninfringement or invalidity unless the defendant objectively has a "reasonable apprehension that it will face an infringement suit." *Jervis B. Webb Co. v. Southern Sys., Inc.*, 742 F.2d 1388, 1398 (Fed.Cir.1984). The existence of a sufficiently concrete dispute between the parties, however, vanishes when subsequent events render the threat of infringement nonexistent. *See Super Sack Mfg. Corp. v. Chase Packaging Corp.*, 57 F.3d 1054, 1058 (Fed.Cir.1995).

[2] 3. Nonetheless, a court is not automatically denied jurisdiction over coun-

terclaims upon the withdrawal of an allegation of infringement.

> In a typical case where the patentee institutes an action for infringement and the alleged infringer counterclaims that the patent is invalid and unenforceable and/or non-infringed, courts will allow the action to go forward on the counterclaim even if the patentee voluntarily dismisses the charge of infringement or stipulates to the non-infringement.

Akzona, Inc. v. E.I. du Pont de Nemours & Co., 662 F.Supp. 603, 619 (D.Del.1987). For the court to maintain jurisdiction, however, the defendant must "establish[ ] by a preponderance of the evidence ... that it has a reasonable apprehension that it will be sued" on the nonasserted claims. *Shell Oil Co. v. Amoco Corp.,* 970 F.2d 885, 887 (Fed.Cir.1992). The Federal Circuit has established a two-part test to determine if a party is in reasonable apprehension of being sued by a patent holder on a particular claim:

> There must be both (1) an explicit threat or other action by the patentee, which creates a reasonable apprehension on the part of the declaratory plaintiff that it will face an infringement suit, and (2) present activity which could constitute infringement or concrete steps taken with the intent to conduct such activity.

BP Chems, Ltd. v. Union Carbide Corp., 4 F.3d 975, 978 (Fed.Cir.1993).

[3] 4. In the case at bar, Thermo maintains a reasonable apprehension of an infringement suit on the nonasserted claims. Biacore's citation to *Grain Processing* to illustrate the absence of jurisdiction is misplaced. In *Grain Processing* the Federal Circuit noted that the plaintiff had "abandoned its charge that [defendant] had infringed ... **and ... 'steadfastly refused to assert infringement' of those claims.** There [was] nothing in the record to suggest that [defendant would] be faced with a similar infringement suit in the future." 840 F.2d at 906 (emphasis added); *see also Biogen, Inc. v. Amgen, Inc.,* 913 F.Supp. 35, 40 (D.Mass.1996) (holding that "in light of [the patent holder's] latest representation that it will relinquish forever the right to sue [defendant] on any claims other than [the asserted claims], [defendant's] counterclaim will be dismissed"). In stark contrast, there is no indication in the record at bar that Biacore has stipulated to noninfringement of claims 1–3, 9–11, and 15 of the '161 patent. This court previously has held that the absence of a formal covenant not to sue or a willingness to accept a judgment of noninfringement creates a reasonable apprehension of suit. *See Mobil Oil Corp. v. Advanced Envtl. Recycling Techs., Inc.,* 826 F.Supp. 112, 114 (D.Del.1993). Moreover, the fact that Thermo is currently litigating allegations of infringement as to dependent claims 4 and 5 of the same patent further supports that apprehension. The court, therefore, will retain jurisdiction as to the invalidity of claims 1–3, 9–11, and 15 of the '161 patent.

B. Infringement

[4–6] 5. Biacore contends that Thermo's CM-dextran cuvette, which is used in Thermo's IAsys ™ biosensors, literally infringes claims 4 and 5 of the '161 patent. Biacore's claim is based upon 35 U.S.C. § 271, which provides in relevant part that

> [e]xcept as otherwise provided in this title, whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States ... during the term of the patent therefor, infringes the patent.

35 U.S.C. § 271(a). The Federal Circuit has set forth a two-step analysis for determining whether there is infringement:

> First, the claims must be correctly construed to determine the scope of the claims. Second, the claims must be compared to the accused device.

Kahn v. General Motors Corp., 135 F.3d 1472, 1476 (Fed.Cir.1998). "To establish literal infringement, a plaintiff must demonstrate that every limitation in the claim is literally met by the accused device." *Id.*

In other words, literal infi when the claim, as constru reads on the accused devi *Engel Indus. v. Lockform* 1398, 1405 (Fed.Cir.1996) may not be avoided simpl tures or components not claims. *See Loctite Cor Ltd.,* 781 F.2d 861, 865 *overruled on other ground AB v. Implant Innovation* 1059 (Fed.Cir.1998). Plair den of demonstrating by a of the evidence that "eve the claim is literally met device." *Kahn,* 135 F.3d a

1. **Claim Const**

[7–9] 6. It is the cou obligation to construe as the meaning of language ent claim." *Markman v. V ments, Inc.,* 52 F.3d 967 1995). The principles of tion are well established begins with the claim lang fines the scope of the cl *Prods., Inc. v. Central T Family Ctr.,* 99 F.3d 156 1996). In analyzing clair court must employ "norm tax," *Eastman Kodak C Tire & Rubber Co.,* 114 (Fed.Cir.1997), for "[a] cla in accordance with the pre grammar," *In re Hyatt,* 7 (Fed.Cir.1983). The cour cribe to any technical term "the meaning that it wou persons experienced in t invention, unless it is ap patent and the prosecution inventor used the term meaning." *Hoechst Celan Chems, Ltd.,* 78 F.3d 157 1996).

7. In order to give con language, the court also specification. The Federa plained that

IES

light of [the patent hold-
sentation that it will relin-
: right to sue [defendant]
other than [the asserted
nt's] counterclaim will be
stark contrast, there is no
record at bar that Biacore
to noninfringement of
and 15 of the '161 patent.
ously has held that the
ial covenant not to sue or
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ates a reasonable appre-
See Mobil Oil Corp. v.
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Motors Corp., 135 F.3d
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limitation in the claim
he accused device." *Id.*

In other words, literal infringement exists when the claim, as construed by the court, reads on the accused device exactly. *See Engel Indus. v. Lockformer Co.*, 96 F.3d 1398, 1405 (Fed.Cir.1996). Infringement may not be avoided simply by adding features or components not required by the claims. *See Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 865 (Fed.Cir.1985), *overruled on other grounds, Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059 (Fed.Cir.1998). Plaintiff has the burden of demonstrating by a preponderance of the evidence that "every limitation of the claim is literally met by the accused device." *Kahn*, 135 F.3d at 1476.

1. Claim Construction

[7-9] 6. It is the court's "power and obligation to construe as a matter of law the meaning of language used in the patent claim." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed.Cir. 1995). The principles of claim construction are well established. The exercise begins with the claim language, which defines the scope of the claim. *See York Prods., Inc. v. Central Tractor Farm & Family Ctr.*, 99 F.3d 1568, 1572 (Fed.Cir. 1996). In analyzing claim language, the court must employ "normal rules of syntax," *Eastman Kodak Co. v. Goodyear Tire & Rubber Co.*, 114 F.3d 1547, 1553 (Fed.Cir.1997), for "[a] claim must be read in accordance with the precepts of English grammar," *In re Hyatt*, 708 F.2d 712, 714 (Fed.Cir.1983). The court also must ascribe to any technical term used in a claim "the meaning that it would be given by persons experienced in the field of the invention, unless it is apparent from the patent and the prosecution history that the inventor used the term with a different meaning." *Hoechst Celanese Corp. v. BP Chems, Ltd.*, 78 F.3d 1575, 1578 (Fed.Cir. 1996).

7. In order to give context to the claim language, the court also must review the specification. The Federal Circuit has explained that

> [t]he specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication. As we have repeatedly stated, "[c]laims must be read in view of the specification, of which they are a part." The specification contains a written description of the invention which must be clear and complete enough to enable those of ordinary skill in the art to make and use it. Thus, the specification is always relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of the disputed term.

Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed.Cir.1996) (citations omitted).

8. The last source of intrinsic evidence relevant to claim construction is the prosecution history of the patent where it is in evidence. The prosecution history contains the complete record of all the proceedings before the PTO, "including any express representations made by the applicant regarding the scope of the claims." *Id.* at 1583. The prosecution history, therefore, "is often of critical significance in determining the meaning of the claims." *Id.*

[10] 9. The court also may consider, in its discretion, extrinsic evidence "to assist in its construction of the written document." *Markman*, 52 F.3d at 981. In most instances, however, extrinsic evidence of claim meaning is improper. *See Vitronics Corp.*, 90 F.3d at 1582. "Extrinsic evidence consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Neither the patent's prosecution history nor any extrinsic evidence considered can "enlarge, diminish, or vary" the limitations in the claims. *Id.*

10. **Product-by-process claims.** As an initial matter, Thermo argues that claims 4 and 5 of the '161 patent are product-by-

process claims that incorporate the "process steps" disclosed in claim 1. Thermo contends that the claim language supports this argument. According to Thermo, claim 4, which incorporates the limitations of claim 1, requires that the dextran hydrogel disclosed be formed through a two-step progression: first, the dextran "is bound to a surface," and then the bound dextran "is activated to contain" both charged and reactive groups. (D.I. 115 at 3–7) Thermo argues that such a construction is consistent with the specification, which broadly describes first attaching dextran to the surface and then activating the bound dextran for purposes of binding ligands. (PX 1, col. 6, lns. 43–47; *see also* PX 1, col. 9, lns. 45, 51, 54–56) Relying on the Federal Circuits's decision in *Atlantic Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834, 846–47 (Fed.Cir.1992), Thermo contends that these process terms serve as limitations that must be proven in order to find infringement.

11. The product—product-by-process claim dichotomy is not absolute or clear cut in application. Product-by-process claims are characterized as being devoid of significant structural description of the final article, instead relying, at least in part, on a description of "the process used to obtain [the claimed invention]" to define it. *Mentor Corp. v. Coloplast, Inc.*, 998 F.2d 992, 997 (Fed.Cir.1993). By contrast, in product claims the article is defined in terms of structural characteristics only. The mere use in a claim of structural or characterizing terms derived from processes or methods, however, does not prevent a claim from being considered a true product claim. *See Application of Hughes*, 496 F.2d 1216, 1219 (C.C.P.A.1974); *In Application of Garnero*, 56 C.C.P.A. 1289, 412 F.2d 276, 279 (1969). Nor does the use of a process limitation convert a pure product claim to a product-by-process claim. *See Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed.Cir.1983). Typically, it is the wording of the claim which indicates that it is a product-by-process claim. For example, product-by-process claims employ terms such as "prepared in accordance with," "by the process of," whereby, "product of the process," "resulting from the process of," and "being produced by the process comprising." *See, e.g., In re Thorpe*, 777 F.2d 695, 696 (Fed.Cir.1985); *In re Fessmann*, 489 F.2d 742, 180 U.S.P.Q. 324, 324 (C.C.P.A.1974); *Application of Hughes*, 496 F.2d 1216, 1217 (C.C.P.A.1974); *Scripps Clinic & Research Found. v. Genentech, Inc.*, 666 F.Supp. 1379, 1385 (N.D.Cal.1987); *Johnson & Johnson v. W.L. Gore & Assoc., Inc.*, 436 F.Supp. 704, 709 (D.Del.1977); *Ex parte Edwards*, 231 U.S.P.Q. 981, 982, 1986 WL 83751 (1986).

[11] 12. Consistent with the above, the court concludes that the claims at issue are not product-by-process claims. Claim 1 of the '161 patent contains none of the wording traditionally associated with product-by process claims. (¶ 37)[42] Despite Thermo's contentions to the contrary, the phrases "which is bound" and "activated to contain" reflect structural limitations not the process by which the claimed invention is obtained. Nor is there anything in the record to indicate that Biacore distinguished the claimed invention from the prior art based on the novelty of the invention's process. Accordingly, claims 4 and 5, which depend in part from claim 1, are best characterized as pure product claims since the disclosed invention is described by its structure rather than how it is made. As such, claims 4 and 5 may encompass identical products formed by different processes.

13. **Preamble limitation.** The parties do not contest the interpretation of any particular term in the claims of the '161 patent. Instead, they contest the limitation, if any, imposed by the phrase in the preambles to independent claims 1 and 15 "suitable for use in a biosensor." Biacore argues that the phrase defines the inven-

42. The indicated paragraphs refer to Part II, Findings of Fact.

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[12, 13] 14. "[A] claim preamble has the import that the claim as a whole suggests for it." *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620 (Fed.Cir.1995). Generally, a claim preamble, when read in the context of the entire claim, recites claim limitations only if "the claim cannot be read independently of the preamble and the preamble must be read to give meaning to the claim or is essential to point out the invention." *Marston v. J.C. Penney Co.*, 353 F.2d 976, 986 (4th Cir.1965) (citing *Kropa v. Robie*, 38 C.C.P.A. 858, 187 F.2d 150 (1951)). Thus, "if a claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett–Packard Co.*, 182 F.3d 1298, 1305 (Fed.Cir.1999) (quoting *Kropa*, 187 F.2d at 152).

> Indeed, when discussing the "claim" in such a circumstance, there is no meaningful distinction to be drawn between the claim preamble and the rest of the claim, for only together do they comprise the "claim." If, however, the body of the claim fully and intrinsically sets forth the complete invention, including all of its limitations, and the preamble offers no distinct definition of any of the claimed invention's limitations, but rather merely states, for example, the purpose or intended use of the invention, then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation.

Id.

[14] 15. In the case at bar, the preamble statement "suitable for use in a biosensor" does not merely state a purpose or intended use for the claimed structure. Rather, the phrase informs the construction of the remainder of the claims by defining the matrix coating. The body of the claims is directed to an article that cannot be divorced from the intended field of use. It is only under the conditions imposed by the phrase "suitable for use in a biosensor" that the elements of the claims perform the functions by which they are defined. Thus, the statement at issue is "necessary to give life, meaning, and vitality" to the claims. The phrase is "meshed with the ensuing language of the claim" because it defines the conditions under which the matrix coating is to be employed. *Id.* Those conditions must be such that the charged groups actually function to bring about a concentration of oppositely-charged ligands that are then covalently bound via the reactive groups. The statement further requires that the quantity of charged groups be that which would bring about a sufficient concentration of biomolecules to produce a useful signal for biosensor purposes. Consequently, the claims can be understood only in the context of this preamble statement, which constitutes a limitation on the claims.

16. With this construction in mind, the court now turns to the issue of infringement.

2. Comparison of the Claims to the Accused Device

[15] 17. Claim 4 of the '161 patent depends from claim 3 and, therefore, includes all of the limitations set forth in claims 1–3. (¶ 42) Accordingly, it is directed to a matrix coating comprising a dex-

tran hydrogel that is bound to a surface and via which a desired ligand can be bound. (¶¶ 37–42) Said hydrogel is activated to contain charged groups for bringing about a concentration of oppositely-charged ligands and reactive groups for covalently binding said concentrated ligands to the matrix coating. (¶ 41) Based on the findings of fact and the court's claim construction, Thermo's CM-dextran cuvette, which is employed in its IAsys ™ biosensors, falls within the literal scope of claim 4 of the '161 patent. Thermo's CM-dextran cuvette utilizes a three-dimensional matrix suitable for use in a biosensor. (D.I. 96 at 3–4; ¶¶ 90–94) Said matrix coating comprises a dextran hydrogel that is attached to the cuvette's surface and via which ligands can be bound. (D.I. 96 at 3–4; ¶¶ 93, 105) The dextran hydrogel in Thermo's CM-dextran cuvette is activated to contain charged groups for bringing about a concentration of oppositely-charged biomolecules and reactive groups for covalently binding said concentrated biomolecules. (¶¶ 93, 105) Thus, each element of claim 4 is present in Thermo's CM-dextran cuvette. The fact that Thermo's process for making the accused cuvette involves first activating unbound dextran and then binding the dextran derivative to the RM surface does not alter this conclusion as claim 4 does not require a particular sequence of steps. (¶ 93)

18. Claim 5 requires that the charged and reactive groups of the activated dextran hydrogel of claim 4 be carboxyl groups. (¶ 42) Claim 5 further requires that some of these carboxyl groups be in the form of one of a particular group of molecular entities of which reactive esters is one. (¶ 42) Thermo's CM-dextran cuvette contains dextran that has been activated to contain charged and reactive carboxyl groups. (¶ 93) Some, but not all, of these carboxyl groups are converted into reactive succinimide esters. (¶ 93) Accordingly, the court concludes that Thermo's CM-dextran cuvette infringes claims 4 and 5 of the '161 patent.

3. Inducing infringement

[16] 19. Having found direct infringement, the court now turns to Biacore's contention that Thermo induces infringement of the '161 patent. *See Met–Coil Sys. Corp. v. Korners Unlimited, Inc.*, 803 F.2d 684, 687 (Fed.Cir.1986) ("Absent direct infringement of the patent claims there can be neither contributory infringement, nor inducement of infringement") (citations omitted). The patent statute provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "A person induces infringement under § 271(b) by actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 675 (Fed.Cir.1990). The level of knowledge or intent required is "actual intent to cause the acts which constitute the infringement." *Hewlett–Packard Co. v. Bausch & Lomb, Inc.*, 909 F.2d 1464, 1469 (Fed.Cir. 1990). Although proof of intent is necessary, direct evidence is not required; rather, circumstantial evidence may suffice. *See Moleculon Research Corp. v. CBS, Inc.*, 793 F.2d 1261, 1272 (Fed.Cir.1986).

[17] 20. Biacore argues that Thermo's marketing and sales of its IAsys ™ biosensor induce the use of the infringing CM-dextran cuvette. (D.I. 111 at 16–17) Specifically, Biacore avers that Thermo induces infringement under § 271(b) by providing its customers with: (1) IAsys ™ biosensors; (2) instructions for using the CM-dextran cuvettes in the devices; (2) manuals instructing how to convert some but not all of the carboxyl groups on the CM-dextran to succinimide esters for purposes of electrostatically concentrating ligands into the dextran matrix and covalently binding the ligands so concentrated when the CM-dextran cuvette is used in the IAsys ™ biosensor; and (3) application notes and promotional literature demonstrating the benefits and uses of the IAsys ™ biosensor. (D.I. 111 at 17) Thermo does not refute Biacore's proffer, except to

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not literally infringe claim
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C. Validity

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1. 35 U.S.C. § 102—A

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argue that its CM-dextran cuvette does not literally infringe claims 4 and 5 of the '161 patent.

21. The evidence of record demonstrates that Thermo intended to cause, and caused, its customers to infringe the patent at issue. Thermo actively marketed the infringing CM-dextran cuvette, sold a biosensor system in which the infringing cuvette could be employed, and produced and provided to its customers manuals instructing them to use the cuvette in a manner that infringes claims 4 and 5 of '161 patent. (¶ 105) While so doing, Thermo was acutely aware of the patent at issue. (¶ 97) The record further indicates, and the parties do not appear to dispute, that Thermo's customer did employ the cuvettes in a manner consistent with Thermo's instructions. Accordingly, the court finds that Thermo intentionally induced direct infringement of claims 4 and 5 of the '161 patent under § 271(b).

C. Validity

[18–20] 22. "A patent is presumed valid, and the burden of proving invalidity, whether under § 112 or otherwise, rests with the challenger. Invalidity must be proven by facts supported by clear and convincing evidence." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed.Cir. 1988). The issue of obviousness is a question of law; however, a determination of obviousness is based on factual inquiries. *See, e.g., In re Goodman*, 11 F.3d 1046, 1049–50 (Fed.Cir.1993); *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582 (Fed.Cir.1996). Anticipation and the adequacy of the written description, on the other hand, are questions of fact. *See, e.g., Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158 (Fed.Cir.1998); *Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir.1995).

1. 35 U.S.C. § 102—Anticipation

[21] 23. Anticipation is established if every element of a properly construed claim is present in a single prior art reference. *See id.; see also PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1566 (Fed.Cir.1996); *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed.Cir.1991). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic & Research Found.*, 927 F.2d at 1576.

> In determining whether a patented invention is anticipated, the claims are read in the context of the patent specification in which they arise and in which the invention is described. If needed to impart clarity or avoid ambiguity, the prosecution history and the prior art may also be consulted in order to ascertain whether the patentee's invention is novel or was previously known to the art.

Glaverbel Societe Anonyme, 45 F.3d at 1554.

[22] 24. Extrinsic evidence has a limited scope in determining anticipation. Although it may be used "to explain the disclosure of a reference," extrinsic evidence is of "limited scope and probative value" since "anticipation requires that all aspects of the claimed invention were already described in a single reference." *Scripps Clinic & Research Found.*, 927 F.2d at 1576. Thus, extrinsic evidence may not be used to "prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention ...." *Id.* Thus, extrinsic evidence of the knowledge of one of ordinary skill in the art is relevant in situations where

> the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges.

Id. at 1569. Accordingly, extrinsic evidence may be used to explain but not expand the meaning of a reference. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed.Cir.1991).

[23] 25. Anticipation may be established if a missing claim element, although not explicitly present in the reference, is necessarily inherent in it. *See Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347 (Fed.Cir.1999). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Id.* Thus, a "gap in [a] reference may be filled with recourse to extrinsic evidence." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1267–68 (Fed.Cir.1991). Such evidence, however, "must make clear that the missing descriptive matter is necessarily present" in the asserted anticipatory reference. *Id.* "Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristic or functioning of the prior art." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed.Cir.1999).

[24] 26. In the instant action, Thermo argues that, with the exception of claim 5,[43] all of the '161 patent claims at issue are anticipated by four separate prior art references, each standing alone: the '470 patent, the Onyezili article, the Mandenius reference, and the Scouten paper. Thermo's anticipation argument, however, rests upon the court's adoption of Thermo's construction of the claims, i.e., that the claims require that the structure disclosed in the '161 patent only be capable of concentrating and covalently binding ligands, not that it be employed under conditions where concentration actually occurs. It is undisputed that none of the asserted anticipatory references teach the use of charged groups for bringing about a concentration of oppositely-charged biomolecules as required by claims 1 and 15. (¶¶ 48, 51–52, 56–57, 62) Nor do the references inform that ionic concentration should be such that electrostatic concentration can be achieved. (¶¶ 48, 51–52, 56–57, 62) As a result, none of the cited references teach reactive groups that function to covalently bind biomolecules having been electrostatically concentrated. (¶¶ 48, 51–52, 56–57, 62) That the matrix coatings disclosed in the prior art references may, or may not, have incorporated within them charged groups capable of attracting and concentrating oppositely-charged biomolecules under the proper conditions is insufficient to anticipate the claims as the court has construed them.

27. The question then arises whether these claim limitations are inherent in the references' disclosures. As previously noted, a prior art reference may anticipate when the claim limitations, although not explicitly disclosed, are nonetheless inherent in it. *See MEHL/Biophile Int'l Corp.*, 192 F.3d at 1365. The Federal Circuit explained the operation of inherency in anticipation as follows:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference .... In *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (CCPA 1981) (quoting *Hansgirg v. Kemmer*, 26 C.C.P.A. 937, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (1939)) provides:
>
> > Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. [Citations omitted]. If, however, the dis-

43. Thermo concedes that the limitations of claim 5 are not fully met by any of the asserted anticipatory references but argues that these limitations would have been "in the art" at the time of the invention. (D.I. 107 at 840–01, 848–49)

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closure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

Continental Can Co., 948 F.2d at 1268–69 (alterations in original); *accord MEHL/Biophile Int'l Corp*, 192 F.3d at 1365; *Finnigan Corp. v. International Trade Commission*, 180 F.3d 1354, 1365 (Fed.Cir.1999).

28. The structures disclosed in the references cited as anticipatory by Thermo do not function in accordance with the claimed limitations. (¶¶ 48, 51–52, 56–57, 62) Nor are the claimed limitations a necessary consequence of the prior art teachings. An individual utilizing the methods disclosed in the prior art references, therefore, could do so without necessarily employing the conditions required to take advantage of the charged groups, if any, in the matrix coating to concentrate the desired ligands prior to covalent binding. The possibility that conditions allowing for concentration by charge might be utilized by one employing the disclosed procedures is not legally sufficient to show anticipation. *See In re Rijckaert*, 9 F.3d 1531, 1534 (Fed.Cir.1993); *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A.1981). "Occasional results are not inherent." *MEHL/Biophile Int'l Corp.*, 192 F.3d at 1365. Dr. Scouten's conclusory allegations—that it would have been apparent to one of ordinary skill in the art not only that the matrix coatings taught in the prior art references possess charged groups but also the conditions necessary to take advantage of electrostatic concentration prior to covalent binding—are insufficient to establish anticipation. (¶ 64) These assertions lack the kind of support in the record needed for proof of invalidity by clear and convincing evidence. Moreover, they do not establish that the asserted references "necessarily function" in accordance with the claimed limitations. Accordingly, the '470 patent, the Onyezili article, the Mandenius reference, and the Scouten paper do not disclose every element of the asserted claims. The court concludes that Thermo has failed to prove that claims 1–5, 9–11, and 15 of the '161 patent are invalid for anticipation.

2. 35 U.S.C. § 103—Obviousness

29. Thermo contends that claims 1–5, 9–11, and 15 of the '161 patent are invalid for obviousness under 35 U.S.C. § 103. Specifically, Thermo argues that, when considered in light of the Charged Concentration References, the Onyezili reference or the Mandenius reference in combination with either the Akanuma reference or the Scouten survey article renders the asserted claims obvious.

30. A patent is invalid under 35 U.S.C. § 103

> if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Obviousness under § 103 is a legal conclusion based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; and (3) the level of ordinary skill in the pertinent art. *See Graham v. John Deere Co.*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). "Objective evidence such as commercial success, copying, or long-felt need, is relevant, and when present must be considered." *Glaverbel Societe Anonyme*, 45 F.3d at 1555 (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–1539 (Fed.Cir.1983)); *see also B.F. Goodrich Co.*, 72 F.3d at 1582.

31. "[T]he burden of showing, by clear and convincing evidence, the invalidity of the [patent] claims ... is especially difficult when the prior art was before the PTO examiner during prosecution of the application." *Hewlett–Packard Co.*, 909 F.2d at 1467. Where there is "no PTO view ... on obviousness in view of [the

asserted] references[,] ... [the] burden of proof ... is more easily carried." *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 905 (Fed.Cir.1985). At all times, the burden of proof on invalidity remains with the party challenging the patent. *See Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375 (Fed.Cir.1986); *American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1358 (Fed.Cir. 1984).

[25] 32. When obviousness is based on prior art references, "there must be a showing of a suggestion or motivation to modify the teachings" of those references. *B.F. Goodrich Co.*, 72 F.3d at 1582. This suggestion to modify the art need not be expressly stated in the references; rather, the test is "whether it would have been obvious to select specific teachings and combine them as did the applicant." *In re Dance*, 160 F.3d 1339, 48 U.S.P.Q.2d 1635, 1637 (Fed.Cir.1998). The test is "met by identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention." *Id.* Hindsight reconstruction and/or "the blueprint drawn by the inventor," *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed.Cir.1985), may not be used "to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention," *In re Fine*, 837 F.2d 1071, 1075 (Fed.Cir.1988); *see also Kahn v. General Motors Corp.*, 135 F.3d 1472, 1479 (Fed.Cir.1998) (stating that "[o]bviousness may not be established using hindsight"). "'[T]he question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311 (Fed.Cir.1992) (quoting *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1462 (Fed.Cir.1984)); *accord In re Fine*, 837 F.2d at 1074–75; *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed.Cir.1984).

[26] 33. **Scope and Content of the Prior Art.** A threshold question is whether any or all of the publications identified by Thermo should be characterized as "prior art." Prior art has been defined as "knowledge that is available, including what would be obvious from it, at a given time, to a person of ordinary skill in an art." *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1453 (Fed.Cir. 1984). The parties do not dispute that all of the references identified by Thermo are within the same field as that of the patented invention and were publicly available more than one year prior to the priority date. (¶ 44) It is undisputed, therefore, that the asserted references are, in fact, prior art to the '161 patent.

34. **The Differences Between the Claims and the Prior Art.** Once the prior art is identified, the focus of the analysis shifts to identifying the differences between the claimed invention and the prior art. *See Gardner v. TEC Sys., Inc.*, 725 F.2d 1338, 1345 (Fed.Cir.1984); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 717 (Fed.Cir.1991) ("When analyzing a patent claim for obviousness the claim should be considered as a whole, but the [principal] differences between the [patented] claim and the prior art need to be identified.") Once these differences are ascertained, the analysis centers on the ultimate legal question, "whether these differences are such that the invention as a whole would have been obvious to one of ordinary skill in the art at the time of the invention." *TEC Sys., Inc.*, 725 F.2d at 1345.

[27] 35. The question at bar is whether, in light of the Charged Concentration References, the teachings of either the Onyezili reference or the Mandenius reference when considered with the teachings of the Akanuma reference or the Scouten survey article, show each and every element required by the asserted claims of the '161 patent and suggest the reasonableness of their combination. Based upon the findings of fact, the court concludes

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that the references in combination do not render the claims obvious. Both the Onyezili and Mandenius references instruct the use of an ostensibly inert dextran matrix[44] in order to "eliminate" or "bypass" nonspecific binding. (¶¶ 48, 51, 55) Accordingly, these references do not teach (1) the use of charged groups for electrostatically concentrating ligands and (2) reactive groups for covalently binding ligands having been so concentrated. (¶¶ 51–52, 56–57) These deficiencies are not cured by either the Scouten survey article or the Akanuma reference, both of which merely describe activation chemistries capable of imparting onto a hydrogel matrix negatively charged carboxyl groups, some of which are in the form of reactive hydrazides or reactive esters. (¶¶ 65, 66–67) Although these references may teach the incorporation of charged groups into a hydrogel matrix, neither instructs, either alone or in combination with the Onyezili and Mandenius references, the use of those groups to concentrate oppositely-charged biomolecules.

36. On the other hand, the Charged Concentration References do suggest, in the context of affinity-based systems,[45] the combination in a matrix coating of charged and reactive groups in order to enhance ligand immobilization. (¶¶ 68–73) There is nothing, however, in the Onyezili and Mandenius references that "fairly suggests" the desirability of the modification to be inferred from the Charged Concentration References and the ability to incorporate that modification via the activation chemistries disclosed in the Scouten survey article and the Akanuma reference. Neither the Onyezili nor the Mandenius reference suggests the benefits of utilizing a charged matrix in the context of a biosensor system. Rather, as noted above, both references instruct the use of a noncharged, inert matrix in order to avoid nonspecific binding. (¶¶ 51, 55) To that extent, both the Onyezili and Mandenius references "teach away" from the asserted combination of prior art references since "a person of ordinary skill, upon reading the reference[s], would be … led in a direction divergent from the path that was taken by the [patentee]." *In re Gurley,* 27 F.3d 551, 553 (Fed.Cir.1994); *see also In re Burckel,* 592 F.2d 1175, 1179 (C.C.P.A. 1979).

[28] 37. Nor is there any inference in the prior art that a beneficial result would be achieved by such a combination. Nonspecific binding was an obstacle facing researchers attempting to develop a functional biosensor. (¶ 13) At the time of the invention, the literature concerning affinity chromatography, as well as the Onyezili and Mandenius references, stressed the need for an inert matrix in order to avoid nonspecific adsorption. (¶¶ 51, 55, 78–80) Thus, the prior art warned against incorporating charged groups in the matrix coating. Thermo's own researchers confirmed this thinking when they expressed concern that the presence of charged carboxyl groups in the dextran matrix would lead to nonspecific binding. (¶ 91) They did not recognize the beneficial effect of using charged groups in conjunction with reactive groups. (¶¶ 89, 91) Only the '161 patent's disclosure suggests the success to be achieved by such a combination. The absence of evidence indicating that one

44. That dextran may have a slight, inherent negative charge is irrelevant to the analysis since the researchers who authored these articles employed the polysaccharide expressly believing it would reduce nonspecific binding. Thus, the Onyezili and Mandenius references teach the use of an inert or noncharged matrix.

45. The Crook patent does make reference to the use in a biosensor of a polymeric matrix containing both charged and reactive groups. (DX 540, col. 3, lns. 51–58) Isolated statements in a patent directed to a polymeric matrix having a structure that differs greatly from that claimed in the '161 patent does not constitute proof of motivation to combine. *See In re Fine,* 837 F.2d at 1075; *Interconnect Planning Corp.,* 774 F.2d at 1138.

skilled in the art[46] would be motivated to combine the asserted references to achieve the claimed invention suggests that the combination is nothing more than hindsight reconstruction and, as such, cannot establish obviousness.

38. **Secondary Considerations.** Objective indicia of nonobviousness must be considered before a conclusion on obviousness is made. *See WMS Gaming, Inc. v. International Game Tech.*, 184 F.3d 1339, 1359 (Fed.Cir.1999); *Hybritech*, 802 F.2d at 1380; *Cable Elec. Prods., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1026 (Fed.Cir. 1985) (stating that secondary considerations must be considered "always 'not just when the decisionmaker remains in doubt after reviewing the art.' ") (quoting *Stratoflex, Inc.*, 713 F.2d at 1539). Such considerations " 'may be the most probative and cogent evidence in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.' " *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 957 (Fed.Cir.1997) (quoting *Stratoflex, Inc.*, 713 F.2d at 1538–39). The patentee bears the burden of establishing that a nexus exists between the objective evidence offered to show nonobviousness and the merits of the claimed features of the invention. *WMS Gaming Inc.*, 184 F.3d at 1359.

39. In the instant action, the secondary considerations provide support for a finding that Thermo has failed to carry its burden. After six years of development and research, Biacore's predecessor overcame the salient problems facing biosensor researchers and successfully marketed the first commercially available, real-time, label-free, affinity-based biosensor in 1990, thus satisfying a long recognized need. (¶ 85) The BIAcore™ system was favorably received and praised by those in the field. (¶ 86) Even Dr. Davies recognized that the matrix coating claimed in the PCT was "inventive."[47] (¶ 101) For a number of years, Thermo, or its predecessors, also sought to develop an affinity-based biosensor, entering the race in 1987. (¶ 87) After four years of experimenting with a number of surface materials and chemistries, none of which yielded a surface capable of immobilizing the requisite concentration of ligands, Thermo began utilizing the activated dextran hydrogel matrix set forth in the PCT,[48] eventually affixing the

46. There are six factors a court should consider in determining the level of ordinary skill in the art: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) the prior art solutions; (4) the rapidity of innovation; (5) the sophistication of the technology at issue; and (6) the educational level of active workers in the field. *See Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449–50 (Fed.Cir.1986). In the case at bar, the parties disagree as to the focus of the patent at issue. Biacore argues that the '161 patent is directed to biosensors; Thermo, on the other hand, contends that the patent's focus is ligand immobilization.

Consistent with its interpretation of the '161 patent, Thermo argues that one of ordinary skill in the art need not have experience with biosensors. (D.I. 106 at 794–96; D.I. 107 at 886) Thermo concedes, however, that such experience would be useful. (D.I. 106 at 794–96) Specifically, Thermo argues that the person of ordinary skill in the art would have a Ph.D. in organic chemistry or biochemistry with a solid work background in ligand immobilization. (D.I. 106 at 794–96) Biacore does not offer an alternative description of one of skill in the art.

The '161 patent is directed to a matrix coating "suitable for use in a biosensor." Accordingly, for purposes of this action, the court concludes that the person of ordinary skill in the art as of November 10, 1988 would have had a Ph.D. in organic chemistry or biochemistry with a solid work background in ligand immobilization as it relates to biosensor technology.

47. Thermo attempts to discredit Dr. Davies' characterization of the claimed invention, arguing that "[i]t is evident that Dr. Davies must have been unaware of the Charged Concentration References when he wrote these words because these references describe this very feature." (D.I. 116 at 17; D.I. 112 at 32–33) Thermo goes on to question Dr. Davies' status as one of ordinary skill in the art. (D.I. 11 at 17)

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matrix to the RM surface using a methodology equivalent to that set forth in the application.[49] (¶¶ 89–94) Thermo's copying of the claimed dextran matrix in light of its failure to develop an alternative technology despite years of experimentation is indicative of the nonobviousness of the claimed invention.

40. Biacore cites to the commercial success of the BIAcore ™ system in further support of its nonobviousness contention. When a patentee asserts commercial success as evidence of nonobviousness, it bears the burden of establishing a nexus between the proven success and the merits of the invention. *See Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed.Cir.1988). Where, as here, "the thing that is commercially successful is not coextensive with the patented invention—for example, if the patented invention is only a component of a commercially successful machine or process—the patentee must show *prima facie* a legally sufficient relationship between that which is patented and that which is sold." *Id.* If the patentee satisfies this burden, the challenger must demonstrate that the commercial success was due to extraneous factors other than the patented invention. *Id.* at 1392.

41. Thermo contends that Biacore's commercial success is associated with the X–R–Y monolayer disclosed in the PCT and '828 patent, not the claimed invention. (D.I. 112 at 28–29; D.I. 116 at 16–17) This does not explain, however, the fact that sales of Thermo's dextran cuvettes, like the sale of Biacore's dextran chips, far exceeds the sales of its other cuvettes, none of which employ the X–R–Y monolayer technology.[50] (¶ 86) Rather, the sales are better explained by the "historic significance" attributed to the CM-dextran matrix as a sensor surface. (D.I. 105 at 550; D.I. 106 at 631–32, 626) Thermo's own advertising describes the CM-dextran cuvettes as the "original sensor surface for biomolecular interactive analysis and hence the most extensively studied and versatile." (D.I. 96 at 3; ¶ 86) Although there are no applications for which CM-dextran is the sole option, its features endow it with advantages that are not met by any other single surface type currently available. (D.I. 169 at 101591; D.I. 105 at 547–48; D.I. 106 at 665; ¶ 106) Moreover, despite Thermo's conclusory allegation that any or all of the patented aspects of Biacore's biosensors may have contributed to their commercial success, it was the dextran matrix that Thermo copied when developing its own IAsys ™ biosensor. (¶¶ 90–94) Accordingly, the court concludes that Biacore has demonstrated a nexus between the claimed invention and the commercial success of its biosensors. Thus, the proven success of the BIAcore ™ system weighs in favor of a finding of nonobviousness.

42. In light of the test set out in *Graham*, the court concludes, after examining the prior art and secondary considerations of nonobviousness, that Thermo has failed to prove by clear and convincing evidence that the '161 patent is invalid on obviousness grounds. The claimed invention is several steps removed from the information presented in the prior art references.

3. 35 U.S.C. § 112

43. The Patent Act requires that a patent specification contain (1) an enabling disclosure; (2) a sufficient written descrip-

May 1990, the same month the PCT application was published, but did not begin experimenting with hydrogels until June 1991.

49. Thermo contends that the PCT claims a dextran hydrogel attached via an X–R–Y monolayer to the metal surface of an SPR biosensor not the CM-dextran hydrogel matrix per se. Accordingly, Thermo argues that its "'copying' of an unclaimed feature is not evidence of nonobviousness." (D.I. 117 at 17; D.I. 112 at 29–31). The court disagrees. *See* discussion *infra* at Part III.C.3.

50. The fact that CM-dextran cuvettes are not reusable generally to the same degree as are other types of cuvettes manufactured by Thermo does not account for the large discrepancy in sales. (D.I. 105 at 548; D.I. 106 at 638–41, 642–43)

tion of the claimed invention; and (3) a disclosure of the best mode of carrying out the invention. The relevant statutory language appears in the first paragraph of § 112 of the Patent Act:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[29] 44. **Written Description.** For a later-filed patent to be entitled to the filing date of an earlier patent, the disclosure of the earlier patent must comply with the written description requirement. *See Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572–73 (Fed.Cir.1997). To satisfy this requirement, the disclosure of the earlier-filed application "must reasonably convey to one of skill in the art that the inventor possessed the later-claimed subject matter at the time the patent application was filed." *Tronzo*, 156 F.3d at 1158; *see also Vas–Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563–64 (Fed.Cir.1991) (stating that the written description requirement is "broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." (emphasis in original)); *Hoechst Celanese Corp. v. BP Chem. Ltd.*, 844 F.Supp. 336, 340 (S.D.Tex.1994) ("[T]he test for the written description requirement is not whether a skilled artisan would have known that lithium iodide was 'suitable' in similar processes; the test is whether the artisan would have known, from reading the description, that the inventor of the '73 application did know of this suitability—and hence had possession of this invention." (emphasis in original)). For possession to be demonstrated, a disclosure must "describ[e] the invention[ ] with all its claimed limitations." *Lockwood*, 107 F.3d at 1572.

> While the meaning of terms, phrases, or diagrams in a disclosure is to be explained or interpreted from the vantage point of one skilled in the art, all the limitations must appear in the specification. The question is not whether a claimed invention is an obvious variant of that which is disclosed in the specification. Rather, a prior application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.

Id.; see also In re Alton, 76 F.3d 1168, 1172 (Fed.Cir.1996) (stating that in order to satisfy the written description requirement a patent must " 'clearly allow persons of ordinary skill in the art to recognize that [the patentee] invented what is claimed.' " (quoting *In re Gosteli*, 872 F.2d 1008, 1012 (Fed.Cir.1989))). The claimed invention, however, need not be described *in ipsis verbis* in order to satisfy the written description requirement. *See Application of Lukach*, 58 C.C.P.A. 1233, 442 F.2d 967, 969 (1971).

[30] 45. The written description requirement is separate and distinct from the enablement requirement. *See Vas–Cath Inc.*, 935 F.2d at 1563–64. A specification that enables the practice of an invention as broadly as it is claimed necessarily need not describe the claimed invention. *See id.* at 1561. As the Federal Circuit's predecessor court, the Court of Customs and Patent Appeals ("CCPA"), explained:

> [W]here the specification discusses only compound A and contains no broadening language of any kind ... [t]his might very well enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B, and C has not been described.

Application of DiLeone, 58 C.C.P.A. 925, 436 F.2d 1404, 1405 n. 1 (1971) (emphasis in original). "That a person skilled in the

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Id. at 1384.

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art might realize from reading the disclosure that such a step is possible is not sufficient indication to that person that the step is part of the applicant's invention." *In re Winkhaus,* 527 F.2d 637, 640 (C.C.P.A.1975) (emphasis in original). This does not mean, however, that a claimed invention cannot broaden the literal aspects of an earlier-filed application. In this regard, the CCPA in *In re Smythe,* 480 F.2d 1376 (C.C.P.A.1973) posed the following hypothetical:

> If the original specification of a patent application on the scales of justice disclosed only a 1–pound "lead weight" as a counterbalance to determine the weight of a pound of flesh, we do not believe the applicant should be prevented, by the so-called "description requirement" of the first paragraph of § 112, or the prohibition against new matter of § 132, from later claiming the counterbalance as a "metal weight" or simply as a 1–pound "weight," although both "metal weight" and "weight" would indeed be progressively broader than "lead weight," including even such an undisclosed, but obviously art-recognized equivalent, "weight" as a pound of feathers. The broader claim language would be permitted because the description of the use and function of the lead weight as a scale counterbalance in the whole disclosure would immediately convey to any person skilled in the scale art the knowledge that the applicant invented a scale with a 1–pound counterbalance weight, regardless of its composition.

Id. at 1384.

[31] 46. Likewise, the CCPA recognized "a subtle distinction between a written description adequate to support a claim under § 112 and a written description sufficient to anticipate its subject matter under § 102(b)." *Vas–Cath, Inc.,* 935 F.2d at 1562 (emphasis in original) (citing *Application of Lukach,* 58 C.C.P.A. 1233, 442 F.2d 967). In *Application of Lukach,* the CCPA found that the patent application at issue was not entitled to the filing date of the grandparent application as the earlier filing did not sufficiently describe the later-claimed invention, but that the British counterpart to the grandparent application anticipated the claimed subject matter. *See Application of Lukach,* 442 F.2d at 969. The CCPA stated in this regard that

> the description of a single embodiment of broadly claimed subject matter constitutes a description of the invention for anticipation purposes (*see, e.g., In re Ruscetta,* 255 F.2d 687, 45 C.C.P.A. 968 (1958)), whereas the same information in a specification might not alone be enough to provide a description of that invention for purposes of adequate disclosure.

Id. at 970. Accordingly, a parent or grandparent application's disclosure can be prior art against, and anticipate the claims of, a later-filed application containing broader claims while still not describing the claimed invention so as to allow the later-claimed invention to assert the parent's filing date. *See, e.g., Application of DiLeone,* 436 F.2d at 1405–06; *In re Ahlbrecht,* 58 C.C.P.A. 848, 435 F.2d 908, 910–12 (1971); *In re Ruscetta,* 45 C.C.P.A. 968, 255 F.2d 687; *see also Chester v. Miller,* 906 F.2d 1574, 1577 (Fed.Cir.1990); *In re Gosteli,* 872 F.2d 1008 (Fed.Cir.1989); *Application of Lukach,* 442 F.2d at 968–70.

[32, 33] 47. Compliance with the written description requirement is a question of fact that must be determined on a case-by-case basis. *See Vas–Cath Inc.,* 935 F.2d at 1562; *In re Wertheim,* 541 F.2d 257, 262 (C.C.P.A.1976) ("the primary consideration is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure."). In order to succeed, a challenger must provide clear and convincing evidence that persons skilled in the art would not recognize in the disclosure a description of the claimed invention. *See In re Alton,* 76 F.3d at 1175.

Thermo contends that the '828 patent's specification does not provide sufficient

support for the broad claims of the '161 patent and, thus, the claims are entitled only to a filing date of May 10, 1993. As such, Thermo argues, the claims of the '161 patent are anticipated by the PCT. The question at bar, therefore, is whether Thermo has provided clear and convincing evidence that persons skilled in the art would not recognize that the patentees had possession of the claimed invention as of November 10, 1988.

[34] 48. Thermo argues that the specification of the '828 patent does not disclose the invention's applicability to nonmetal surfaces and/or to hydrogels bound directly to the underlying surface. (D.I. 112 at 33–39) It is axiomatic that the claims of a patent may be broader than the specific embodiment disclosed in the specification. *See, e.g., In re Peters,* 723 F.2d 891, 893 (Fed.Cir.1983). Thus, that the written description of the '828 patent repeatedly refers to metal surfaces, lacks an example of a hydrogel attached to a nonmetal surface, and provides a preferred embodiment in which a hydrogel is bound to a metal surface via an X–R–Y monolayer is not, in and of itself, dispositive. Likewise, the fact that, during prosecution of the '828 patent, the applicants distinguished the prior art in part on the presence in the claimed invention of a densely packed X–R–Y monolayer and discussed in the specification the limitations inherent in a particular method of attaching an organic polymer directly to a metal biosensor surface, does not render the written description insufficient on its face. Rather, the focus is on whether a skilled artisan reading the description of the '828 patent would conclude that the inventors knew the hydrogel matrix disclosed was suitable for use on both metal and nonmetal surfaces and could be directly attached thereto. As to that issue, Thermo's expert offered no opinion.

[35] 49. Reading the specification in light of what the '161 patent claims state and considering it against the background of the prior art, the court finds that Thermo has failed to carry its burden. The essence of the original disclosure is a sensing surface suitable for use in a biosensor comprised of a bound and activated, three-dimensional hydrogel matrix that is capable of selectively coupling the desired ligands.[51] The written description details the hydrogel matrix's versatility and notes its applicability to a variety of types of biosensors, not just those employing metal surfaces.[52] (*see, e.g.,* PX 4, col. 1, lns. 16–20, 40; col. 3, lns. 13–15, 22–25, 40–45; col. 4, lns. 8–13; col. 5, lns. 29–41; col. 8, lns. 31–36) In fact, the record indicates that Thermo's researchers copied the matrix coating disclosed in the PCT because they recognized it would work for the purposes they intended, i.e., in a biosensor employing a nonmetal surface, and attached it to the RM surface using known surface chemistries. (¶ 90) Moreover, the use of the disclosed matrix to increase "liquid density per area unit" and its functionalization to electrostatically concentrate and covalently bind ligands, thereby enhancing the measuring signal, is well documented in the specification. (*see, e.g.,* PX 4, col. 5, lns. 29–41; col. 6, lns. 33–35, 43–51) Furthermore, during the relevant time period, the use of hydrogels in biosensors generally and the means of attaching them to metal, as well as nonmetal surfaces, was well known. (¶¶ 75–76) Given this understanding and the description of the use and function of the hydrogel matrix in the disclosure, the court concludes that Thermo has failed to prove by clear and convincing evidence that the disclosure does not con-

51. Although the disclosure and claims teach that the desired ligands may be bound directly to the X–R–Y monolayer, the majority of the specification as well as the preferred embodiment and the claims are directed to the binding of ligands by an activated hydrogel matrix coupled to an X–R–Y monolayer.

52. SPR technology itself is not limited to metal surfaces. (PX 39: "[S]urface plasmons exist in the boundary of a solid (metal or semi conductor) whose electrons behave like those of a quasi-free electron gas.")

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IV. DAMAGES

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50. In sum, the court concludes that Thermo has not carried its burden that the asserted claims of the '161 patent are invalid.

IV. DAMAGES

1. Based on the foregoing, it is the court's conclusion that Thermo infringes claims 4 and 5 of the '161 patent. Accordingly, Biacore is entitled to relief for Thermo's infringement. Biacore asserts that it is entitled to lost profit damages, enhanced damages, prejudgment interest, attorneys' fees, and injunctive relief.

A. Lost Profit Damages

2. The standard for damages for patent infringement is set forth in 35 U.S.C. § 284. Section 284 provides that a patent owner whose patent has been infringed is entitled to "damages adequate to compensate for the infringement, but in no event less than a reasonable royalty for the use made of the invention by the infringer, together with the interests and costs as fixed by the court." Damages for infringement have been broadly defined as the "difference between the patentee's pecuniary condition after the infringement, and what [the patentee's] condition would have been if infringement had not occurred." *King Instruments Corp. v. Perego,* 65 F.3d 941, 948 (Fed.Cir.1995). The reasonable royalty provision in the statute provides the "floor below which damage awards may not fall." *Rite–Hite Corp. v. Kelley Co.,* 56 F.3d 1538, 1544 (Fed.Cir.1995).

[36] 3. In the instant action, Biacore seeks lost profits damages. In order to be entitled to lost profits, as opposed to royalties, a patentee must show a reasonable probability that it would have made sales of the infringing product "but for" the infringement. *See Rite–Hite,* 56 F.3d at 1545; *BIC Leisure Prods. v. Windsurfing Int'l Inc.,* 1 F.3d 1214, 1218 (Fed.Cir.1993). Thus, a patent owner is not required to demonstrate causation with absolute certainty. *See Kaufman Co. v. Lantech, Inc.,* 926 F.2d 1136, 1141 (Fed.Cir.1991) ("A patentee need not negative every possibility that the purchaser might not have bought another product other than his absent the infringement.").

[37, 38] 4. A patentee can show "but for" causation by means of the four-factor test set forth in *Panduit Corp. v. Stahlin Bros. Fibre Works, Inc.,* 575 F.2d 1152 (6th Cir.1978), though this is not an exclusive means for showing entitlement to lost profits damages. *See Rite–Hite,* 56 F.3d at 1545. The *Panduit* test requires a patentee to show (1) demand for the patented product, (2) the absence of acceptable non-infringing alternatives, (3) the marketing and manufacturing capability to exploit the demand, and (4) the amount of profit it would have made but for the infringement. *See Panduit Corp.,* 575 F.2d at 1156. Satisfaction of these factors allows the court to reasonably infer that the claimed lost profits were caused by the infringing sales. *See Rite–Hite,* 56 F.3d at 1545. The same inference is possible upon a showing that the patentee and the infringer are the only suppliers present in the market. *See Kaufman Co.,* 926 F.2d at 1141. "Consequently, when the fact situation compels the reasonableness of the inference via both courses, the inference approaches conclusiveness." *Id.* Once the patentee establishes the reasonableness of the inference, the burden "shifts to the infringer to show that the inference is unreasonable for some or all of the lost sales." *Rite–Hite,* 56 F.3d at 1545.

5. The first factor of the *Panduit* test presupposes that the demand for the patentee's product and the infringer's product is interchangeable. *See BIC Leisure Prods.,* 1 F.3d at 1218. This factor requires, therefore, that the patent owner and the infringer sell substantially the same product. *See id.* at 1219. "If the products are not sufficiently similar to

compete in the same market for the same customers, the infringer's customers would not necessarily transfer their demand to the patent owner's product in the absence of the infringer's product." *Id.*

6. Similarly, the second *Panduit* factor assumes that the patentee and the infringer sell substantially similar products in the same market. *See id.* This factor requires that any proffered alternative compete in the same market for the same customer as the infringer's product. *See id.* In order for an alleged alternative to be acceptable to an infringer's customers, it "'must not have a disparately higher price than or possess characteristics significantly different from the patented product.'" *Id.* (quoting *Kaufman Co.,* 926 F.2d at 1142).

> A product on the market which lacks the advantages of the patented product can hardly be termed a substitute acceptable to the customer who wants those advantages. Accordingly, if purchasers are motivated to purchase because of particular features available only from the patented product, products without such features—even if otherwise competing in the marketplace—would not be acceptable noninfringing substitutes.

Standard Havens Prods., Inc. v. Gencor Indus., 953 F.2d 1360, 1373 (Fed.Cir.1991). An acceptable alternative, however, need not possess all of the features of the patented invention as it is not required to "represent an embodiment of the invention." *SmithKline Diagnostics v. Helena Labs.,* 926 F.2d 1161, 1166 (Fed.Cir.1991). Thus, proof that there are no acceptable noninfringing alternatives requires a showing either that "(1) the purchasers in the market place generally were willing to buy the patented product for its advantages, or (2) the specific purchasers of the infringing product purchased on that basis." *Id.*

[39] 7. Where, as here, the patentee seeks damages on components sold with a patented apparatus, the "entire market value rule" is applied. *See Rite–Hite,* 56 F.3d at 1549. This rule "permits recovery of damages based on the value of a patentee's entire apparatus containing several features when the patent-related feature is the 'basis for customer demand.'" *Id.* The entire market rule is applicable where

> the patented and unpatented components together are "analogous to components of a single assembly," "parts of a complete machine," or "constitute a functional unit," but not where the unpatented components "have essentially no functional relationship to the patented invention and ... may have been sold with an infringing device only as a matter of convenience or business advantage."

Tec Air, Inc. v. Denso Mfg. Michigan Inc., 192 F.3d 1353, 1362 (Fed.Cir.1999).

[40] 8. In the case at bar, it is undisputed that demand exists for both the BIAcore™ and the IAsys™ biosensors. It is equally undisputed that Thermo and Biacore are the only suppliers of optical biosensors capable of performing real-time, label-free kinetic measurements. Although other analytical instruments capable of measuring biomolecular interactions are commercially available, none are capable of performing the range of functions of the BIAcore™ and IAsys™ devices. Thus, the market for optical biosensors of this nature is composed of two suppliers.

9. The patented and unpatented component parts of the BIAcore™ and IAsys™ biosensor systems, respectively, in combination "constitute a functional unit." Those parts, specifically Thermo's CM-dextran cuvette and Biacore's patented dextran chip, however, are not interchangeable between units. The CM-dextran cuvette is suitable for use only in the IAsys™ system while the Biacore dextran chip can be used only in a BIAcore™ biosensor. (¶ 93) Thus, the cuvette and the chip cannot be substituted one for the other. Accordingly, sales of the cuvette and the chip are linked to the sales of their respective biosensor systems, which are not equivalent. Among other differences,

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the BIAcore™ system is far more expensive than the IAsys™ system, it employs a "rapid flow" system rather than a "vibrostirrer" as is found in the IAsys™ biosensor, it is unable because of limitations imposed by the flow system capillaries to analyze whole cells, and it has a smaller active surface on its chip than the IAsys™ does in its cuvette. (D.I. 103 at 120, 134–39; D.I. 508, 529–31, 557–585, 60–62; DX 979; DX 988; ¶¶ 84–85, 102) Moreover, the IAsys™ biosensor is fully operable and functions without the CM-dextran cuvette as other types of cuvettes are available. (¶ 106) Given these differences, the court concludes that Biacore has not met its burden. Although the evidence of record establishes a nexus between the sale of the BIAcore™ and IAsys™ biosensors and the dextran matrix claimed in the '161 patent, it is insufficient to establish the claimed matrix as the "basis for customer demand." [53]

10. The evidence of record also demonstrates that there is no molecular interaction measurable by the IAsys™ system for which the CM-dextran matrix is the sole option. (¶ 106) While the CM-dextran matrix may be more versatile than the other available surfaces, one or more of the nondextran cuvettes are suitable for every application for which customers use the CM-dextran cuvette. (¶ 106) Thus, these cuvettes are acceptable alternatives to the patented invention. In light of the aforementioned differences between the biosensor systems at issue, Biacore has failed to demonstrate there was a reasonable probability that a customer, when faced with a choice between a BIAcore™ system with a dextran chip and a Thermo system sporting an applicable nondextran cuvette, would have chosen the BIAcore™ system. *See SmithKline Diagnostics*, 926 F.2d at 1166 ("[I]f the realities of the market are that others would likely have captured sales made by the infringer, despite a difference in the products, it follows that the 'but for' test is not met."). Accordingly, the court concludes that Biacore has failed to prove by a preponderance of the evidence that it would have made Thermo's sales had there been no infringement.[54] Having so found, a determination of damages based upon a reasonable royalty is required.[55] *See Water Techs. Corp. v. Calco, Ltd.*, 850 F.2d 660, 673–74 (Fed.Cir. 1988).

B. Enhanced Damages—Willful Infringement

[41] 11. Biacore contends that Thermo willfully infringed the '161 patent, warranting enhanced damages and attorneys' fees. Pursuant to § 284, a court may in its discretion "increase the damages up to three times the amount found or assessed." The Federal Circuit has set forth a two-step analysis a court should employ in exercising its discretion:

> First, the fact-finder must determine whether an infringer is guilty of conduct upon which increased damages may be based. If so, the court then determines, exercising its sound discretion, whether, and to what extent, to increase the damages award given the totality of the circumstances.

53. Biacore argues that Thermo's admissions made in opposition to Biacore's request for a preliminary injunction judicially estop Thermo from now arguing that demand for the CM-dextran cuvette is not probative of demand for the patented product. (D.I. 111 at 27-28; D.I. 117 at 13) Review of the record, however, reveals that Thermo's arguments as to the motion for preliminary injunction are not inconsistent with its current position.

54. The court's finding that Biacore demonstrated a nexus between its sales of the BIAcore™ system and its dextran chip is not inconsistent with this conclusion. That Biacore's sales of its biosensor system might be linked to its patented dextran matrix does not establish an entitlement to lost profits damages.

55. Based on the briefing before it, the court declines at this juncture to address the calculation of a reasonable royalty. The court also will defer discussion of prejudgment interest until such time as it rules on the issue of reasonable royalty.

Jurgens v. CBK, Ltd., 80 F.3d 1566, 1570 (Fed.Cir.1996). In evaluating the egregiousness of an infringer's conduct the court must consider factors that render the infringer's conduct more culpable as well as factors that are mitigating or ameliorating. *See Read Corp. v. Portec, Inc.*, 970 F.2d 816, 826 (Fed.Cir.1992); *SRI Int'l v. Advanced Tech. Labs., Inc.*, 127 F.3d 1462, 1468–69 (Fed.Cir.1997). Factors the court may take into consideration when determining whether and to what extent to exercise its discretion include:

> (1) whether the infringer deliberately copied the ideas or design of another, (2) whether the infringer, when he knew of the other's patent protection, investigated the scope of the patent and formed a good-faith belief that it was invalid or that it was not infringed, (3) the infringer's behavior as a party to the litigation, (4) the infringer's size and financial condition, (5) the closeness of the case, (6) the duration of the infringer's misconduct, (7) any remedial action by the infringer, (8) the infringer's motivation for harm, and (9) whether the infringer attempted to conceal its misconduct.

Johns Hopkins Univ. v. CellPro, Inc., 152 F.3d 1342, 1352 n. 16 (Fed.Cir.1998). The ultimate question remains, however, "whether the infringer, acting in good faith and upon due inquiry, had sound reason to believe that it had the right to act in the manner that was found to be infringing." *SRI Int'l*, 127 F.3d at 1464–65. In the instant action, Biacore bears the burden of proving by clear and convincing evidence that Thermo acted willfully in infringing the '161 patent. *See id.* at 1465.

12. It is undisputed that Thermo had knowledge of the PCT when it developed and began marketing its IAsys™ biosensor. (¶ 88) It also is undisputed that the '265 continuation application, which broadened the claims of the '828 patent, was not filed until two months after Thermo gave its first public demonstration of the IAsys™ biosensor at a meeting attended by Biacore representatives. (¶¶ 29, 94–95) The record also establishes that the IAsys™ biosensor had been sold in the United States for over a year before the '161 patent, with its broadened claims, issued and that Thermo became aware of the patent no later than September 7, 1995. (¶ 97)

[42] 13. Actual notice of another's patent rights imposes an affirmative duty of due care upon the potential infringer to avoid infringement. *Electro Med. Sys., S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1056 (Fed.Cir.1994). This duty generally includes "seeking and obtaining competent legal advice before engaging in activity that may result in infringement." *Id.* There is, however, no "absolute requirement that a would-be defendant aware of another's patent obtain its own opinion letter in order to immunize itself from a finding of willful infringement." *Hall v. Aqua Queen Mfg., Inc.*, 93 F.3d 1548, 1555 (Fed.Cir.1996). The Federal Circuit has held, however, "that when an infringer refuses to produce an exculpatory opinion of counsel in response to a charge of willful infringement, an inference may be drawn that either no opinion was obtained or, if an opinion was obtained, it was unfavorable." *Electro Med. Sys.*, 34 F.3d at 1056. Nevertheless, such an inference "does not foreclose consideration of other relevant factors. Possession of a favorable opinion of counsel is not essential to avoid a willfulness determination; it is only one factor to be considered, albeit an important one." *Id.*

[43] 14. Based upon its review of the totality of the circumstances, the court concludes that Biacore has not satisfied its burden of establishing by clear and convincing evidence that Thermo willfully infringed the '161 patent. The evidence of record indicates that prior to the issuance of the '161 patent Thermo copied the hydrogel matrix, but not the X–R–Y technology, disclosed in the PCT. (¶ 93) Thermo made no attempt to conceal from Biacore's predecessor that it had done so, and Biacore never accused Thermo of infringing

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the PCT or its U.S. counterpart, the '828 patent. The record further reveals that once Thermo became aware of the '161 patent it investigated the scope of the patent as well as its validity but made no attempt to redesign its CM-dextran cuvette in order to avoid infringement. (¶¶ 97–100)

15. As noted, Thermo's failure to provide an exculpatory opinion of counsel despite the fact that it sought legal advice from two separate sources is an important factor to consider but is not dispositive. (¶ 99) Although Thermo stipulated that it "does not assert that it had a good-faith belief that the '161 patent was not infringed, invalid or unenforceable[,]" (D.I. 96 at 5), the evidence at bar indicates that the validity of the '161 patent was a close case.[56] The claims of the '161 patent embrace a hydrogel bound by any means to any type of surface while the grandparent application is drawn to a hydrogel bound to a metal surface by an X–R–Y monolayer. (¶ 23–28, 33–43) As evidenced by the voluminous record, Thermo put on a substantial challenge as to whether the generic claims of the '161 patent were obvious or anticipated by the prior art as well as whether the written description of the '828 patent was sufficient to support these broadened claims. Accordingly, the court concludes that Biacore is not entitled to an enhanced damages award.

[44] 16. Likewise, the court declines to find that this case is an "exceptional case" under 35 U.S.C. § 285. Section 285 provides that "in exceptional cases [the court] may award reasonable attorney fees to the prevailing party." The purpose of this section is to compensate "the prevailing party for its monetary outlays in prosecution or defense of a suit where the conduct of the losing party is clearly inequitable." *Multi–Tech, Inc. v. Components, Inc.,* 708 F.Supp. 615, 620 (D.Del.1989). In determining whether to award attorneys' fees, the Federal Circuit teaches that the court must first determine whether the case is exceptional; if it is, then it is within the court's discretion to award reasonable attorneys' fees to the prevailing party. *See J.P. Stevens Co. v. Lex Tex Ltd.,* 822 F.2d 1047, 1050 (Fed.Cir.1987); *Machinery Corp. of America v. Gullfiber AB,* 774 F.2d 467, 470 (Fed.Cir.1985). In general, for a case to be deemed exceptional there must be some finding, by clear and convincing evidence, of willful infringement, inequitable conduct before the PTO, misconduct during the litigation, vexatious or unjustified litigation or some similar exceptional circumstances. *See Advance Transformer Co. v. Levinson,* 837 F.2d 1081, 1085 (Fed.Cir.1988); *Standard Oil Co. v. American Cyanamid Co.,* 774 F.2d 448, 455 (Fed.Cir.1985); *Stevenson v. Sears, Roebuck & Co.,* 713 F.2d 705, 713 (Fed.Cir.1983). In the instant action, the court concludes that Biacore has not satisfied its burden of establishing by clear and convincing evidence that Thermo's actions make this case an exceptional one. Accordingly, the court shall deny Biacore's request for attorneys' fees.

C. Injunctive Relief

[45, 46] 17. Biacore seeks a permanent injunction enjoining Thermo from infringing the '161 patent. Pursuant to 35 U.S.C. § 283, this court is authorized to "grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable." The court is not required to enter an injunction when infringement has been determined. *See, e.g., W.L. Gore & Assocs.,*

56. Biacore contends that in submitting verbatim the claims of the '161 patent as part of its own patent application, Thermo "expressed its belief that the claimed subject matter was patentable over the prior art." (D.I. 111 at 37) Thermo, however, indicated in the amendment to the PTO containing the claims that the claims had been copied from the '161 patent. Thus, the record indicates that Thermo was attempting to provoke an interference action challenging the validity of the '161 patent claims despite the fact that it did not explicitly so state to the examiner.

Inc. v. Garlock, Inc., 842 F.2d 1275, 1281 (Fed.Cir.1988). Rather, a court has broad discretion in deciding whether to grant an injunction and in determining the scope of an injunction. *See Joy Techs. Inc v. Flakt, Inc.*, 6 F.3d 770, 772 (Fed.Cir.1993). As a general rule, however, "an injunction will issue when infringement has been adjudged, absent a sound reason for denying it." *Richardson v. Suzuki Motor Co., Ltd.*, 868 F.2d 1226, 1247 (Fed.Cir.1989). That the injunction might put the infringer out of business does not justify denial of the injunction. *See Windsurfing Int'l, Inc. v. AMF, Inc.*, 782 F.2d 995, 1003 n. 12 (Fed.Cir.1986). In the instant action, there is no sound reason for denying an injunction. Accordingly, the court will grant a permanent injunction preventing Thermo from infringing the '161 patent.

V. CONCLUSION

For the reasons discussed, the court finds that in making, selling, and using IAsys ™ biosensors employing a CM-dextran cuvette defendant Thermo has infringed, and induced infringement of, claims 4 and 5 of the '161 patent in violation of 35 U.S.C. § 271. Further, the court finds the '161 patent valid and enforceable under 35 U.S.C. §§ 102, 103, and 112. As a result of finding infringement, Biacore is entitled to a permanent injunction preventing Thermo from infringing claims 4 and 5 of the '161 patent. In addition, Biacore is entitled to money damages to be calculated based upon a reasonable royalty. Judgment shall be entered accordingly.

KEPNER–TREGOE, INC., Plaintiff,

v.

EXECUTIVE DEVELOPMENT, INC., Defendant.

Civ. No. 97–3473(JAG).

United States District Court,
D. New Jersey.

Dec. 13, 1999.

Publisher of instructional materials for corporate management training programs sued competitor for copyright infringement. On defendant's motion for summary judgment, the District Court, Greenaway, J., held that: (1) suit was barred by laches, and (2) expired copyright was not renewed by copyright registration of wholly derivative work.

Motion granted.

1. Monopolies 🔑**12(16.5)**

Noerr–Pennington doctrine exempts from antitrust liability any legitimate use of courts by private citizens.

2. Copyrights and Intellectual Property 🔑**83(3.1)**

To establish copyright infringement, plaintiff must prove: (1) ownership of valid copyright, and (2) copying of constituent elements of work that are original by defendant.

3. Copyrights and Intellectual Property 🔑**83(3.5)**

Copyright registration certificates issued by Copyright Office comprise prime facie evidence of validity and ownership of material.

4. Copyrights and Intellectual Property 🔑**53(1)**

To establish "substantial similarity," copyright infringement plaintiff must satisfy "extrinsic test," which queries whether there is sufficient similarity between two works in question to conclude that alleged

infringer used copyrighted
his own, and "intrinsic test,'
from lay perspective, wheth
unlawful appropriation of c
terial. 17 U.S.C.A. § 106.

5. Equity 🔑**67**

Laches is equitable
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6. Equity 🔑**72(1)**

In New Jersey, lache
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7. Copyrights and Intelle
🔑**80**

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8. Copyrights and Intelle
🔑**80**

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9. Copyrights and Intelle
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